09/992095

CJC

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 31, 2006

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND 37 CFR 1.323
Docket No. G-091US05DIV
Patent No. 6,989,262

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Stephane Bejanin and Hiroaki Tanaka
Issued	:	January 24, 2006
Patent No.	:	6,989,262
For	:	Plasmin Variants and Uses Thereof

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Should Read:**
Column 26, line 17:	Page 29, line 31:
"86: 9832-8935"	--86: 9832-9835--

Patent Reads:	**Application Reads:**
Column 35, line 63:	Page 41, line 5:
"omithine"	--ornithine--

Patent Reads:	**Application Should Read:**
Column 38, line 38:	Page 44, line 6:
"osetoprotegerin"	--osteoprotegerin--
Column 40, line 22:	Page 46, line 5:
"268 2984-2988"	--268: 2984-2988--

Patent Reads:	**Application Reads:**
Column 52 line 12:	Page 59, line 5:
"Bateman et."	--Bateman *et al.*--
Column 56, line 42:	Page 64, line 7:
"thereof Therefore,"	--thereof. Therefore,--
Column 77, line 25:	Page 88, line 14:
"ethanolamine"	--ethanolarnine--
Column 77, line 32:	Page 88, line 18:
"ethanolamine"	--ethanolarnine--

Patent Reads:	**Application Should Read:**
Column 77, line 47:	Page 88, line 28:
"ration will"	--ratio will--
Column 79, line 20:	Page 90, line 23:
"hplc"	--HPLC--
Column 81, line 56:	Page 93, line 20:
"embrionic"	--embryonic--
Column 93, line 20:	Page 106, line 12:
"fragements"	--fragments--

Patent Reads:	**Application Reads:**
Column 97, line 11:	Page 110, line 15:
"gaccttgca"	--gacccttgca--

Patent Reads:	**Application Reads:**
Column 97, line 24:	Page 110, line 23:
"gaagttcct"	--gaagtttcct--
Column 97, line 28:	Page 110, line 26:
"ccttcccccagc"	--ccttcctcccccagc--
Column 97, line 29:	Page 110, line 26:
"ggacgttgcat"	--ggacgattgcat--
Column 97, line 65:	Page 111, line 11:
"P450 arom"	--P450arom--

Patent Reads:	**Application Should Read:**
Column 102, lines 55-56:	Page 116, line 23:
"Pat. No. 6,124,008/PCT WO98/46289"	--Pat. No. 6,124,008; PCT WO98/46289--
Column 102, line 62:	Page 116, line 28:
"acetablular"	--acetabular--
Column 106, line 20:	Page 120, line 21:
"acceptablely acceptable"	--acceptable--

Patent Reads:	**Application Reads:**
Column 107, line 33:	Page 121, line 33:
"gccgccggcc"	--gccgcggcc--
Column 107, line 35:	Page 121, line 33:
"gtgtcagtagac"	--gtgtcagctagac--
Column 112, line 46:	Page 127, line 23:
"bums"	--burns--
Column 113, line 56:	Page 128, line 33:
"404-0-A11-F"	--40-4-0-A11-F--

Patent Reads:	**Application Should Read:**
Column 117, lines 39-40:	Page 133, line 5:
"yeast Candida alibcans"	--yeast Candida albicans--
Column 118, line 3:	Page 133, line 26:
"be reference"	--by reference--
Column 118, lines 34-35:	Page 134, lines 8-9:
"(e) *Bacteriodes fragilis*; (f) *Bacteriodes gracilis*; (g) *Bacteriodes ureolyticus*;"	--(e) *Bacteroides fragilis*; (f) *Bacteroides gracilis*; (g) *Bacteroides ureolyticus*;--
Column 120, line 6:	Page 135, line 37:
"hetertetrameric"	--heterotetrameric--
Column 120, line 22:	Page 136, line 9:
"hyperfinbrinolysis"	--hyperfibrinolysis--
Column 124, line 47:	Page 141, line 8:
"trangenic"	--transgenic--
Column 125, line 39:	Page 142, line 8:
"87-93 which"	--87-93) which--
Column 131, line 34:	Page 148, line 31:
"(o) Pencillin"	--(o) Penicillin--

Patent Reads:	**Application Reads:**
Column 145, lines 38-39:	Page 164, line 29:
"organic a mine"	--organic amine--

Patent Reads:	**Application Should Read:**
Column 154, line 10:	Page 174, line 13:
"A preferred embodiments"	--A preferred embodiment--
Column 154, line 49:	Page 174, line 37:
"anti-oestrogen"	--anti-estrogen--

Patent Reads:

Column 158, lines 6-7:

"Notebom et al.,"

Application Reads:

Page 178, line 28:

--Noteborn et al.,--

Patent Reads:

Column 159, line 2:

"matrixproteins"

Application Should Read:

Page 179, line 30:

--matrix proteins--

Patent Reads:

Column 160, line 38:

"500721700_204-434-0-H10-F"

Column 160, line 42:

"500721700_204-434-0-H10-F"

Column 161, line 28:

"by for ming"

Application Reads:

Page 181, line 18:

--500721700_204-43-4-0-H10-F--

Page 181, line 20:

--500721700_204-43-4-0-H10-F--

Page 182, line 18:

--by forming--

Patent Reads:

Column 161, line 33:

"comples"

Application Should Read:

Page 182, line 21:

--complex--

Patent Reads:

Column 162, line 45:

"266: 503641"

Application Reads:

Page 183, line 34:

--266: 5036-41--

Patent Reads:

Column 168, lines 54-55:

"such as a. gamma. camera."

Application Should Read:

Page 190, lines 32-33:

--such as a gamma camera.--

Patent Reads:	**Application Reads:**
Column 170, lines 47-48:	Page 192, line 36:
"(serine protease inhibitor)"	--(serine protease inhibitor)--

Patent Reads:	**Application Should Read:**
Column 187, line 32:	Page 211, line 29:
"bums"	--burns--
Column 188, line 65:	Page 213, line 16:
"aquous"	--aqueous--
Column 190, line 30:	Page 215, line 5:
"In other embodiment,"	--In other embodiments,--
Column 193, line 58:	Page 218, line 35:
"Contrarily In contrast"	--Contrarily, in contrast--
Column 193, line 60:	Page 218, line 36:
"(Bernot et alet al.,"	--(Bernot et al.,--
Column 194, line 32:	Page 219, line 23:
"(Li et alet al,"	--(Li et al.,--
Column 195, line 62:	Page 221, line 12:
"More particularity,"	--More particularly,--
Column 197, lines 7-8:	Page 222, line 23:
"347, 83-87"	--347: 83-87--
Column 200, line 34:	Page 226, line 20:
"18(2)263-294"	--18(2): 263-294--
Column 209, line 38:	Page 236, line 23:
"implicated tumor cell"	--implicated in tumor cell--
Column 215, line 40:	Page 243, line 19:
"does not contains"	--does not contain--
Column 224, line 29:	Page 253, line 15:
"forma of"	--forms of--

Patent Reads:	**Application Should Read:**
Column 224, line 36:	Page 253, line 19:
"Am J; Med. Genet."	--Am. J. Med. Genet.--
Column 226, lines 49-50:	Page 256, line 1:
"oligonucleotides probes"	--oligonucleotide probes--
Column 228, lines 29-30:	Page 257, line 34:
"deshydrogenase"	--dehydrogenase--
Column 228, line 41:	Page 258, line 4:
"deshydrogenase"	--dehydrogenase--
Column 231, line 4:	Page 260, line 33:
"musculr hypotonia"	--muscular hypotonia--
Column 231, line 5:	Page 260, lines 33-34:
"3-hydrixidicarboxylic"	--3-hydroxydicarboxylic--
Column 231, lines 52-53:	Page 261, line 26:
"oligonucleotides probes"	--oligonucleotide probes--

Patent Reads:	**Application Reads:**
Column 232, line 13:	Page 262, line 6:
"122421_105-0764-O-HI-F"	--122421_105-076-4-O-HI-F--
Column 232, line 19:	Page 262, line 10:
"122421_105-0764-O-HI-F"	--122421_105-076-4-O-HI-F--
Column 241, line 63:	Page 273, line 1:
"100038_105-0174-0-E4-F,"	--100038-105-017-4-0-E4-F,--
Column 241, line 65:	Page 273, line 1:
"and 100545_105-019-2-E3-F"	--and 100545_105-019-2-0-E3-F--
Column 259, line 31:	Page 292, line 32:
"GATTTCTTC"	--GATTTTTCTTC--
Column 260, line 10:	Page 293, line 20:
"GAAAAAACAT"	--GAAAAAAACAT--

Patent Reads:	**Application Reads:**
Column 260, line 22:	Page 293, line 26:
"CAAAAAAT"	--CAAAAAAAT--

Patent Reads:	**Application Should Read:**
Column 261, line 50:	Page 295, line 9:
"An recent study"	--A recent study--
Column 263, line 18:	Page 296, line 36:
"In additional preferred embodiment"	--In an additional preferred embodiment--
Column 270, line 7:	Page 304, line 26:
"(swissprot accession numberP02749)"	--(swissprot accession number P02749)--
Column 272, line 54:	Page 307, line 30:
"antiphopholid"	--antiphospholid--
Column 272, line 57:	Page 307, line 32:
"antiphopholid"	--antiphospholid--
Column 272, line 59:	Page 307, line 33:
"antiphopholid"	--antiphospholid--
Column 282, lines 10-11:	Page 318, line 10:
"17beta-hydroxysteroids"	--17 beta-hydroxysteroids--
Column 282, line 15:	Page 318, line 12:
"17beta-HSD"	--17 beta-HSD--
Column 289, line 21:	Page 326, line 13:
"0.5MNaCl"	--0.5 M NaCl--

Patent Reads:	**Application Reads:**
Column 290, line 39:	Page 327, line 30:
"270: 467470"	--270: 467-470--

AUG – 7 2006

Patent Reads:	**Application Should Read:**
Column 312, line 58:	Page 354, line 5:
"CH.sub.2"	--CH_2--
Column 312, line 64:	Page 354, line 8:
"Tne such"	--One such--
Column 313, line 41:	Page 354, lines 34-35:
"0.6-1.2 degree. C."	--0.6-1.2° C.--
Column 321, line 20:	Page 363, line 26:
"0.5 .mu.m to 5 .mu.m"	--0.5 μm to 5 μm--
Column 321, line 45:	Page 364, line 5:
"(ETDA)"	--(EDTA)--

Patent Reads:	**Application Reads:**
Column 343, line 62 (SEQ ID NO:77):	Page 388, Table IV, Row 3 (SEQ ID NO:77):
"68 1-832"	--681-832--
Column 343, line 76 (SEQ ID NO:101):	Page 388, Table IV, Row 17 (SEQ ID NO:101):
"98 1-1013"	--981-1013--

Patent Reads:	**Page 4 of Amendment filed April 15, 2005 Reads:**
Column 563, line 41:	Original claim 55, line 1 (renumbered as claim 7):
"consisting of"	--comprising--

Patent Reads:	**Page 2 of Examiner's Supplemental Notice of Allowability dated June 1, 2005 Reads:**
Column 563, line 43:	Original claim 55, line 2 (renumbered as claim 7):
"comprising"	--consisting of--

Column 564, line 40:	Original claim 59, line 2 (renumbered as claim 11) contained two instances of "comprising". The Supplemental Notice of Allowability did not indicate which "comprising" would be replaced with "consisting of". To be consistent with original claims 55 (line 2) and 56 (line 2—changed by the Examiner's Amendment (see Supplemental Notice of Allowability, page 2, last 2 lines)), only the second instance of the word "comprising" should have been replaced with "consisting of". The first instance of the word "comprising" in original claim 59, line 2, should not have been changed to "consisting of".:
"consisting of a carrier"	--comprising a carrier--.

A true and correct copy of pages 59, 64, 88, 110, 111, 121, 127, 128, 164, 178, 181-183, 190, 262, 273, 292, 293, 327, and 388 of the specification as filed, a copy of the Amendment filed April 15, 2005, and a copy of the Supplemental Notice of Allowability dated June 1, 2005, all of which support Applicants' assertion of the errors on the part of the Patent Office, accompany this Certificate of Correction.

The Commissioner is authorized to charge the fee of $100.00 for the amendment to Deposit Account No. 19-0065. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065. Two copies of this letter are enclosed for Deposit Account authorization.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/ehm/sl

Attachments: Copy of pages 59, 64, 88, 110, 111, 121, 127, 128, 164, 178, 181-183, 190, 262, 273, 292, 293, 327, and 388 of the specification; Copy of the Amendment filed April 15, 2005; Copy of the Supplemental Notice of Allowability dated June 1, 2005

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 31, 2006

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND 37 CFR 1.323
Docket No. G-091US05DIV
Patent No. 6,989,262

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Stephane Bejanin and Hiroaki Tanaka
Issued	:	January 24, 2006
Patent No.	:	6,989,262
For	:	Plasmin Variants and Uses Thereof

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

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Column 26, line 17:	Page 29, line 31:
"86: 9832-8935"	--86: 9832-9835--

Patent Reads:	**Application Reads:**
Column 35, line 63:	Page 41, line 5:
"omithine"	--ornithine--

Patent Reads:	**Application Should Read:**
Column 38, line 38:	Page 44, line 6:
"osetoprotegerin"	--osteoprotegerin--
Column 40, line 22:	Page 46, line 5:
"268 2984-2988"	--268: 2984-2988--

Patent Reads:	**Application Reads:**
Column 52 line 12:	Page 59, line 5:
"Bateman et."	--Bateman *et al.*--
Column 56, line 42:	Page 64, line 7:
"thereof Therefore,"	--thereof. Therefore,--
Column 77, line 25:	Page 88, line 14:
"ethanolamine"	--ethanolarnine--
Column 77, line 32:	Page 88, line 18:
"ethanolamine"	--ethanolarnine--

Patent Reads:	**Application Should Read:**
Column 77, line 47:	Page 88, line 28:
"ration will"	--ratio will--
Column 79, line 20:	Page 90, line 23:
"hplc"	--HPLC--
Column 81, line 56:	Page 93, line 20:
"embrionic"	--embryonic--
Column 93, line 20:	Page 106, line 12:
"fragements"	--fragments--

Patent Reads:	**Application Reads:**
Column 97, line 11:	Page 110, line 15:
"gaccttgca"	--gacccttgca--

Patent Reads:	**Application Reads:**
Column 97, line 24:	Page 110, line 23:
"gaagttcct"	--gaagtttcct--
Column 97, line 28:	Page 110, line 26:
"ccttccccagc"	--ccttcctcccccagc--
Column 97, line 29:	Page 110, line 26:
"ggacgttgcat"	--ggacgattgcat--
Column 97, line 65:	Page 111, line 11:
"P450 arom"	--P450arom--

Patent Reads:	**Application Should Read:**
Column 102, lines 55-56:	Page 116, line 23:
"Pat. No. 6,124,008/PCT WO98/46289"	--Pat. No. 6,124,008; PCT WO98/46289--
Column 102, line 62:	Page 116, line 28:
"acetablular"	--acetabular--
Column 106, line 20:	Page 120, line 21:
"acceptablely acceptable"	--acceptable--

Patent Reads:	**Application Reads:**
Column 107, line 33:	Page 121, line 33:
"gccgccggcc"	--gccgcggcc--
Column 107, line 35:	Page 121, line 33:
"gtgtcagtagac"	--gtgtcagctagac--
Column 112, line 46:	Page 127, line 23:
"bums"	--burns--
Column 113, line 56:	Page 128, line 33:
"404-0-A11-F"	--40-4-0-A11-F--

Patent Reads:	**Application Should Read:**
Column 117, lines 39-40:	Page 133, line 5:
"yeast Candida alibcans"	--yeast Candida albicans--
Column 118, line 3:	Page 133, line 26:
"be reference"	--by reference--
Column 118, lines 34-35:	Page 134, lines 8-9:
"(e) *Bacteriodes fragilis*; (f) *Bacteriodes gracilis*; (g) *Bacteriodes ureolyticus*;"	--(e) *Bacteroides fragilis*; (f) *Bacteroides gracilis*; (g) *Bacteroides ureolyticus*;--
Column 120, line 6:	Page 135, line 37:
"hetertetrameric"	--heterotetrameric--
Column 120, line 22:	Page 136, line 9:
"hyperfinbrinolysis"	--hyperfibrinolysis--
Column 124, line 47:	Page 141, line 8:
"trangenic"	--transgenic--
Column 125, line 39:	Page 142, line 8:
"87-93 which"	--87-93) which--
Column 131, line 34:	Page 148, line 31:
"(o) Pencillin"	--(o) Penicillin--

Patent Reads:	**Application Reads:**
Column 145, lines 38-39:	Page 164, line 29:
"organic a mine"	--organic amine--

Patent Reads:	**Application Should Read:**
Column 154, line 10:	Page 174, line 13:
"A preferred embodiments"	--A preferred embodiment--
Column 154, line 49:	Page 174, line 37:
"anti-oestrogen"	--anti-estrogen--

Patent Reads:

Column 158, lines 6-7:

"Notebom et al.,"

Application Reads:

Page 178, line 28:

--Noteborn et al.,--

Patent Reads:

Column 159, line 2:

"matrixproteins"

Application Should Read:

Page 179, line 30:

--matrix proteins--

Patent Reads:

Column 160, line 38:

"500721700_204-434-0-H10-F"

Column 160, line 42:

"500721700_204-434-0-H10-F"

Column 161, line 28:

"by for ming"

Application Reads:

Page 181, line 18:

--500721700_204-43-4-0-H10-F--

Page 181, line 20:

--500721700_204-43-4-0-H10-F--

Page 182, line 18:

--by forming--

Patent Reads:

Column 161, line 33:

"comples"

Application Should Read:

Page 182, line 21:

--complex--

Patent Reads:

Column 162, line 45:

"266: 503641"

Application Reads:

Page 183, line 34:

--266: 5036-41--

Patent Reads:

Column 168, lines 54-55:

"such as a. gamma. camera."

Application Should Read:

Page 190, lines 32-33:

--such as a gamma camera.--

Patent Reads:	**Application Reads:**
Column 170, lines 47-48:	Page 192, line 36:
"(serine protease inhibitor)"	--(serine protease inhibitor)--

Patent Reads:	**Application Should Read:**
Column 187, line 32:	Page 211, line 29:
"bums"	--burns--
Column 188, line 65:	Page 213, line 16:
"aquous"	--aqueous--
Column 190, line 30:	Page 215, line 5:
"In other embodiment,"	--In other embodiments,--
Column 193, line 58:	Page 218, line 35:
"Contrarily In contrast"	--Contrarily, in contrast--
Column 193, line 60:	Page 218, line 36:
"(Bernot et alet al.,"	--(Bernot et al.,--
Column 194, line 32:	Page 219, line 23:
"(Li et alet al,"	--(Li et al.,--
Column 195, line 62:	Page 221, line 12:
"More particularity,"	--More particularly,--
Column 197, lines 7-8:	Page 222, line 23:
"347, 83-87"	--347: 83-87--
Column 200, line 34:	Page 226, line 20:
"18(2)263-294"	--18(2): 263-294--
Column 209, line 38:	Page 236, line 23:
"implicated tumor cell"	--implicated in tumor cell--
Column 215, line 40:	Page 243, line 19:
"does not contains"	--does not contain--
Column 224, line 29:	Page 253, line 15:
"forma of"	--forms of--

Patent Reads:	**Application Should Read:**
Column 224, line 36:	Page 253, line 19:
"Am J; Med. Genet."	--Am. J. Med. Genet.--
Column 226, lines 49-50:	Page 256, line 1:
"oligonucleotides probes"	--oligonucleotide probes--
Column 228, lines 29-30:	Page 257, line 34:
"deshydrogenase"	--dehydrogenase--
Column 228, line 41:	Page 258, line 4:
"deshydrogenase"	--dehydrogenase--
Column 231, line 4:	Page 260, line 33:
"musculr hypotonia"	--muscular hypotonia--
Column 231, line 5:	Page 260, lines 33-34:
"3-hydrixidicarboxylic"	--3-hydroxydicarboxylic--
Column 231, lines 52-53:	Page 261, line 26:
"oligonucleotides probes"	--oligonucleotide probes--

Patent Reads:	**Application Reads:**
Column 232, line 13:	Page 262, line 6:
"122421_105-0764-O-HI-F"	--122421_105-076-4-O-HI-F--
Column 232, line 19:	Page 262, line 10:
"122421_105-0764-O-HI-F"	--122421_105-076-4-O-HI-F--
Column 241, line 63:	Page 273, line 1:
"100038_105-0174-0-E4-F,"	--100038-105-017-4-0-E4-F,--
Column 241, line 65:	Page 273, line 1:
"and 100545_105-019-2-E3-F"	--and 100545_105-019-2-0-E3-F--
Column 259, line 31:	Page 292, line 32:
"GATTTCTTC"	--GATTTTTCTTC--
Column 260, line 10:	Page 293, line 20:
"GAAAAAACAT"	--GAAAAAAACAT--

Patent Reads:	**Application Reads:**
Column 260, line 22:	Page 293, line 26:
"CAAAAAAT"	--CAAAAAAAT--

Patent Reads:	**Application Should Read:**
Column 261, line 50:	Page 295, line 9:
"An recent study"	--A recent study--
Column 263, line 18:	Page 296, line 36:
"In additional preferred embodiment"	--In an additional preferred embodiment--
Column 270, line 7:	Page 304, line 26:
"(swissprot accession numberP02749)"	--(swissprot accession number P02749)--
Column 272, line 54:	Page 307, line 30:
"antiphopholid"	--antiphospholid--
Column 272, line 57:	Page 307, line 32:
"antiphopholid"	--antiphospholid--
Column 272, line 59:	Page 307, line 33:
"antiphopholid"	--antiphospholid--
Column 282, lines 10-11:	Page 318, line 10:
"17beta-hydroxysteroids"	--17 beta-hydroxysteroids--
Column 282, line 15:	Page 318, line 12:
"17beta-HSD"	--17 beta-HSD--
Column 289, line 21:	Page 326, line 13:
"0.5MNaCl"	--0.5 M NaCl--

Patent Reads:	**Application Reads:**
Column 290, line 39:	Page 327, line 30:
"270: 467470"	--270: 467-470--

Patent Reads:	**Application Should Read:**
Column 312, line 58:	Page 354, line 5:
"CH.sub.2"	--CH_2--
Column 312, line 64:	Page 354, line 8:
"Tne such"	--One such--
Column 313, line 41:	Page 354, lines 34-35:
"0.6-1.2 degree. C."	--0.6-1.2° C.--
Column 321, line 20:	Page 363, line 26:
"0.5 .mu.m to 5 .mu.m"	--0.5 μm to 5 μm--
Column 321, line 45:	Page 364, line 5:
"(ETDA)"	--(EDTA)--

Patent Reads:	**Application Reads:**
Column 343, line 62 (SEQ ID NO:77):	Page 388, Table IV, Row 3 (SEQ ID NO:77):
"68 1-832"	--681-832--
Column 343, line 76 (SEQ ID NO:101):	Page 388, Table IV, Row 17 (SEQ ID NO:101):
"98 1-1013"	--981-1013--

Patent Reads:	**Page 4 of Amendment filed April 15, 2005 Reads:**
Column 563, line 41:	Original claim 55, line 1 (renumbered as claim 7):
"consisting of"	--comprising--

Patent Reads:	**Page 2 of Examiner's Supplemental Notice of Allowability dated June 1, 2005 Reads:**
Column 563, line 43:	Original claim 55, line 2 (renumbered as claim 7):
"comprising"	--consisting of--

Column 564, line 40:	Original claim 59, line 2 (renumbered as claim 11) contained two instances of "comprising". The Supplemental Notice of Allowability did not indicate which "comprising" would be replaced with "consisting of". To be consistent with original claims 55 (line 2) and 56 (line 2—changed by the Examiner's Amendment (see Supplemental Notice of Allowability, page 2, last 2 lines)), only the second instance of the word "comprising" should have been replaced with "consisting of". The first instance of the word "comprising" in original claim 59, line 2, should not have been changed to "consisting of".:
"consisting of a carrier"	--comprising a carrier--.

A true and correct copy of pages 59, 64, 88, 110, 111, 121, 127, 128, 164, 178, 181-183, 190, 262, 273, 292, 293, 327, and 388 of the specification as filed, a copy of the Amendment filed April 15, 2005, and a copy of the Supplemental Notice of Allowability dated June 1, 2005, all of which support Applicants' assertion of the errors on the part of the Patent Office, accompany this Certificate of Correction.

The Commissioner is authorized to charge the fee of $100.00 for the amendment to Deposit Account No. 19-0065. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065. Two copies of this letter are enclosed for Deposit Account authorization.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

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Gainesville, FL 32614-2950

FCE/ehm/sl

Attachments: Copy of pages 59, 64, 88, 110, 111, 121, 127, 128, 164, 178, 181-183, 190, 262, 273, 292, 293, 327, and 388 of the specification; Copy of the Amendment filed April 15, 2005; Copy of the Supplemental Notice of Allowability dated June 1, 2005

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 31, 2006

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND 37 CFR 1.323
Docket No. G-091US05DIV
Patent No. 6,989,262

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Stephane Bejanin and Hiroaki Tanaka
Issued	:	January 24, 2006
Patent No.	:	6,989,262
For	:	Plasmin Variants and Uses Thereof

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Should Read:**
Column 26, line 17:	Page 29, line 31:
"86: 9832-8935"	--86: 9832-9835--

Patent Reads:	**Application Reads:**
Column 35, line 63:	Page 41, line 5:
"omithine"	--ornithine--

Patent Reads:	**Application Should Read:**
Column 38, line 38:	Page 44, line 6:
"osetoprotegerin"	--osteoprotegerin--
Column 40, line 22:	Page 46, line 5:
"268 2984-2988"	--268: 2984-2988--

Patent Reads:	**Application Reads:**
Column 52 line 12:	Page 59, line 5:
"Bateman et."	--Bateman *et al.*--
Column 56, line 42:	Page 64, line 7:
"thereof Therefore,"	--thereof. Therefore,--
Column 77, line 25:	Page 88, line 14:
"ethanolamine"	--ethanolarnine--
Column 77, line 32:	Page 88, line 18:
"ethanolamine"	--ethanolarnine--

Patent Reads:	**Application Should Read:**
Column 77, line 47:	Page 88, line 28:
"ration will"	--ratio will--
Column 79, line 20:	Page 90, line 23:
"hplc"	--HPLC--
Column 81, line 56:	Page 93, line 20:
"embrionic"	--embryonic--
Column 93, line 20:	Page 106, line 12:
"fragements"	--fragments--

Patent Reads:	**Application Reads:**
Column 97, line 11:	Page 110, line 15:
"gaccttgca"	--gacccttgca--

Patent Reads:	**Application Reads:**
Column 97, line 24:	Page 110, line 23:
"gaagttcct"	--gaagtttcct--
Column 97, line 28:	Page 110, line 26:
"ccttcccccagc"	--ccttcctcccccagc--
Column 97, line 29:	Page 110, line 26:
"ggacgttgcat"	--ggacgattgcat--
Column 97, line 65:	Page 111, line 11:
"P450 arom"	--P450arom--

Patent Reads:	**Application Should Read:**
Column 102, lines 55-56:	Page 116, line 23:
"Pat. No. 6,124,008/PCT WO98/46289"	--Pat. No. 6,124,008; PCT WO98/46289--
Column 102, line 62:	Page 116, line 28:
"acetablular"	--acetabular--
Column 106, line 20:	Page 120, line 21:
"acceptablely acceptable"	--acceptable--

Patent Reads:	**Application Reads:**
Column 107, line 33:	Page 121, line 33:
"gccgccggcc"	--gccgcggcc--
Column 107, line 35:	Page 121, line 33:
"gtgtcagtagac"	--gtgtcagctagac--
Column 112, line 46:	Page 127, line 23:
"bums"	--burns--
Column 113, line 56:	Page 128, line 33:
"404-0-A11-F"	--40-4-0-A11-F--

Patent Reads:	**Application Should Read:**
Column 117, lines 39-40:	Page 133, line 5:
"yeast Candida alibcans"	--yeast Candida albicans--
Column 118, line 3:	Page 133, line 26:
"be reference"	--by reference--
Column 118, lines 34-35:	Page 134, lines 8-9:
"(e) *Bacteriodes fragilis*; (f) *Bacteriodes gracilis*; (g) *Bacteriodes ureolyticus*;"	--(e) *Bacteroides fragilis*; (f) *Bacteroides gracilis*; (g) *Bacteroides ureolyticus*;--
Column 120, line 6:	Page 135, line 37:
"hetertetrameric"	--heterotetrameric--
Column 120, line 22:	Page 136, line 9:
"hyperfinbrinolysis"	--hyperfibrinolysis--
Column 124, line 47:	Page 141, line 8:
"trangenic"	--transgenic--
Column 125, line 39:	Page 142, line 8:
"87-93 which"	--87-93) which--
Column 131, line 34:	Page 148, line 31:
"(o) Pencillin"	--(o) Penicillin--

Patent Reads:	**Application Reads:**
Column 145, lines 38-39:	Page 164, line 29:
"organic a mine"	--organic amine--

Patent Reads:	**Application Should Read:**
Column 154, line 10:	Page 174, line 13:
"A preferred embodiments"	--A preferred embodiment--
Column 154, line 49:	Page 174, line 37:
"anti-oestrogen"	--anti-estrogen--

Patent Reads:

Column 158, lines 6-7:

"Notebom et al.,"

Application Reads:

Page 178, line 28:

--Noteborn et al.,--

Patent Reads:

Column 159, line 2:

"matrixproteins"

Application Should Read:

Page 179, line 30:

--matrix proteins--

Patent Reads:

Column 160, line 38:

"500721700_204-434-0-H10-F"

Column 160, line 42:

"500721700_204-434-0-H10-F"

Column 161, line 28:

"by for ming"

Application Reads:

Page 181, line 18:

--500721700_204-43-4-0-H10-F--

Page 181, line 20:

--500721700_204-43-4-0-H10-F--

Page 182, line 18:

--by forming--

Patent Reads:

Column 161, line 33:

"comples"

Application Should Read:

Page 182, line 21:

--complex--

Patent Reads:

Column 162, line 45:

"266: 503641"

Application Reads:

Page 183, line 34:

--266: 5036-41--

Patent Reads:

Column 168, lines 54-55:

"such as a. gamma. camera."

Application Should Read:

Page 190, lines 32-33:

--such as a gamma camera.--

Patent Reads:	**Application Reads:**
Column 170, lines 47-48:	Page 192, line 36:
"(serine protease inhibitor)"	--(serine protease inhibitor)--

Patent Reads:	**Application Should Read:**
Column 187, line 32:	Page 211, line 29:
"bums"	--burns--
Column 188, line 65:	Page 213, line 16:
"aquous"	--aqueous--
Column 190, line 30:	Page 215, line 5:
"In other embodiment,"	--In other embodiments,--
Column 193, line 58:	Page 218, line 35:
"Contrarily In contrast"	--Contrarily, in contrast--
Column 193, line 60:	Page 218, line 36:
"(Bernot et alet al.,"	--(Bernot et al.,--
Column 194, line 32:	Page 219, line 23:
"(Li et alet al,"	--(Li et al.,--
Column 195, line 62:	Page 221, line 12:
"More particularity,"	--More particularly,--
Column 197, lines 7-8:	Page 222, line 23:
"347, 83-87"	--347: 83-87--
Column 200, line 34:	Page 226, line 20:
"18(2)263-294"	--18(2): 263-294--
Column 209, line 38:	Page 236, line 23:
"implicated tumor cell"	--implicated in tumor cell--
Column 215, line 40:	Page 243, line 19:
"does not contains"	--does not contain--
Column 224, line 29:	Page 253, line 15:
"forma of"	--forms of--

Patent Reads:	**Application Should Read:**
Column 224, line 36:	Page 253, line 19:
"Am J; Med. Genet."	--Am. J. Med. Genet.--
Column 226, lines 49-50:	Page 256, line 1:
"oligonucleotides probes"	--oligonucleotide probes--
Column 228, lines 29-30:	Page 257, line 34:
"deshydrogenase"	--dehydrogenase--
Column 228, line 41:	Page 258, line 4:
"deshydrogenase"	--dehydrogenase--
Column 231, line 4:	Page 260, line 33:
"musculr hypotonia"	--muscular hypotonia--
Column 231, line 5:	Page 260, lines 33-34:
"3-hydrixidicarboxylic"	--3-hydroxydicarboxylic--
Column 231, lines 52-53:	Page 261, line 26:
"oligonucleotides probes"	--oligonucleotide probes--

Patent Reads:	**Application Reads:**
Column 232, line 13:	Page 262, line 6:
"122421_105-0764-O-HI-F"	--122421_105-076-4-O-HI-F--
Column 232, line 19:	Page 262, line 10:
"122421_105-0764-O-HI-F"	--122421_105-076-4-O-HI-F--
Column 241, line 63:	Page 273, line 1:
"100038_105-0174-0-E4-F,"	--100038-105-017-4-0-E4-F,--
Column 241, line 65:	Page 273, line 1:
"and 100545_105-019-2-E3-F"	--and 100545_105-019-2-0-E3-F--
Column 259, line 31:	Page 292, line 32:
"GATTTCTTC"	--GATTTTTCTTC--
Column 260, line 10:	Page 293, line 20:
"GAAAAAACAT"	--GAAAAAAACAT--

Patent Reads:	**Application Reads:**
Column 260, line 22:	Page 293, line 26:
"CAAAAAAT"	--CAAAAAAAT--

Patent Reads:	**Application Should Read:**
Column 261, line 50:	Page 295, line 9:
"An recent study"	--A recent study--
Column 263, line 18:	Page 296, line 36:
"In additional preferred embodiment"	--In an additional preferred embodiment--
Column 270, line 7:	Page 304, line 26:
"(swissprot accession numberP02749)"	--(swissprot accession number P02749)--
Column 272, line 54:	Page 307, line 30:
"antiphopholid"	--antiphospholid--
Column 272, line 57:	Page 307, line 32:
"antiphopholid"	--antiphospholid--
Column 272, line 59:	Page 307, line 33:
"antiphopholid"	--antiphospholid--
Column 282, lines 10-11:	Page 318, line 10:
"17beta-hydroxysteroids"	--17 beta-hydroxysteroids--
Column 282, line 15:	Page 318, line 12:
"17beta-HSD"	--17 beta-HSD--
Column 289, line 21:	Page 326, line 13:
"0.5MNaCl"	--0.5 M NaCl--

Patent Reads:	**Application Reads:**
Column 290, line 39:	Page 327, line 30:
"270: 467470"	--270: 467-470--

Patent Reads:	**Application Should Read:**
Column 312, line 58:	Page 354, line 5:
"CH.sub.2"	--CH_2--
Column 312, line 64:	Page 354, line 8:
"Tne such"	--One such--
Column 313, line 41:	Page 354, lines 34-35:
"0.6-1.2 degree. C."	--0.6-1.2° C.--
Column 321, line 20:	Page 363, line 26:
"0.5 .mu.m to 5 .mu.m"	--0.5 μm to 5 μm--
Column 321, line 45:	Page 364, line 5:
"(ETDA)"	--(EDTA)--

Patent Reads:	**Application Reads:**
Column 343, line 62 (SEQ ID NO:77):	Page 388, Table IV, Row 3 (SEQ ID NO:77):
"68 1-832"	--681-832--
Column 343, line 76 (SEQ ID NO:101):	Page 388, Table IV, Row 17 (SEQ ID NO:101):
"98 1-1013"	--981-1013--

Patent Reads:	**Page 4 of Amendment filed April 15, 2005 Reads:**
Column 563, line 41:	Original claim 55, line 1 (renumbered as claim 7):
"consisting of"	--comprising--

Patent Reads:	**Page 2 of Examiner's Supplemental Notice of Allowability dated June 1, 2005 Reads:**
Column 563, line 43:	Original claim 55, line 2 (renumbered as claim 7):
"comprising"	--consisting of--

Column 564, line 40:	Original claim 59, line 2 (renumbered as claim 11) contained two instances of "comprising". The Supplemental Notice of Allowability did not indicate which "comprising" would be replaced with "consisting of". To be consistent with original claims 55 (line 2) and 56 (line 2—changed by the Examiner's Amendment (see Supplemental Notice of Allowability, page 2, last 2 lines)), only the second instance of the word "comprising" should have been replaced with "consisting of". The first instance of the word "comprising" in original claim 59, line 2, should not have been changed to "consisting of".:
"consisting of a carrier"	--comprising a carrier--.

A true and correct copy of pages 59, 64, 88, 110, 111, 121, 127, 128, 164, 178, 181-183, 190, 262, 273, 292, 293, 327, and 388 of the specification as filed, a copy of the Amendment filed April 15, 2005, and a copy of the Supplemental Notice of Allowability dated June 1, 2005, all of which support Applicants' assertion of the errors on the part of the Patent Office, accompany this Certificate of Correction.

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Gainesville, FL 32614-2950

FCE/ehm/sl

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signatures in databases using any computer method known to those skilled in the art. Searchable databases include Prosite [Hofmann *et al.*, (1999) Nucl. Acids Res. 27:215-219; Bucher and Bairoch (1994) Proceedings 2nd International Conference on Intelligent Systems for Molecular Biology. Altman et al, Eds., pp53-61, AAAIPress, Menlo Park], Pfam [Sonnhammer, *et al.*, (1997) Proteins. 28(3):405-20; Henikoff *et al.*, (2000) Electrophoresis 21(9):1700-6; Bateman *et al.*, (2000) Nucleic Acids Res. 28(1):263-6], Blocks [Henikoff *et al.*, (2000) Nucleic Acids Res. 28(1):228-30], Print [Attwood *et al.*, (1996) Nucleic Acids Res. 24(1):182-8], Prodom [Sonnhammer and Kahn, (1994) Protein Sci. 3(3):482-92; Corpet *et al.* (2000) Nucleic Acids Res. 28(1):267-9], Sbase [Pongor *et al.* (1993) Protein Eng. 6(4):391-5; Murvai *et al.*, (2000) Nucleic Acids Res. 28(1):260-2], Smart [Schultz *et al.* (1998) Proc Natl Acad Sci USA 95, 5857-5864], Dali/FSSP [Holm and Sander (1996) Nucleic Acids Res. 24(1):206-9, Holm and Sander (1997) Nucleic Acids Res. 25(1):231-4 and Holm and Sander (1999) Nucleic Acids Res. 27(1):244-7], HSSP [Sander and Schneider (1991) Proteins. 9(1):56-68.], CATH [Orengo *et al.*, (1997) Structure. 5(8):1093-108; Pearl *et al.*, (2000) Biochem Soc Trans. 28(2):269-75], SCOP [Murzin *et al.*, (1995) J Mol Biol. 247(4):536-40; Lo Conte *et al.*, (2000) Nucleic Acids Res. 28(1):257-9], COG [Tatusov *et al.* (1997), Science, 278, 631 :637 and Tatusov *et al.* (2000), Nucleic Acids Res. 28(1):33-6], specific family databases and derivatives thereof [Nevill-Manning *et al.*, (1998) Proc. Natl. Acad. Sci. U S A. 95, 5865-5871; Yona, *et al*, (1999), Proteins. 37(3):360-78; Attwood *et al.*, (2000) Nucleic Acids Res. 28(1):225-7], each of which disclosures are hereby incorporated by reference in their entireties. For a review on available databases, see issue 1 of volume 28 of Nucleic Acid Research (2000), which disclosure is hereby incorporated by reference in its entirety.

Epitopes and Antibody Fusions:

A preferred embodiment of the present invention is directed to epitope-bearing polypeptides and epitope-bearing polypeptide fragments. These epitopes may be "antigenic epitopes" or both an "antigenic epitope" and an "immunogenic epitope". An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response *in vivo* when the polypeptide is the immunogen. On the other hand, a region of polypeptide to which an antibody binds is defined as an "antigenic determinant" or "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes [*see, e.g.*, Geysen *et al.*, (1984), Proc. Natl. Acad. Sci. U.S.A. 81:3998-4002, which disclosure is hereby incorporated by reference in its entirety]. It is particularly noted that although a particular epitope may not be immunogenic, it is nonetheless useful since antibodies can be made to both immunogenic and antigenic epitopes. When the antigen is a polypeptide, it is customary to classify epitopes as being linear (i.e., composed of a contiguous sequence of amino acids repeated along the polypeptide chain) or nonlinear (i.e., composed of amino acids brought into proximity as a result of the folding of the polypeptide chain). Nonlinear epitopes are also called "conformational" because they arise through the folding of the polypeptide chain into a particular conformation, i.e.,

al., (1991), J. Immunol. 147:60-69; US Patents 5,573,920, 4,474,893, 5,601,819, 4,714,681, 4,925,648; Kostelny *et al.*, (1992), J. Immunol. 148:1547-1553, which disclosures are hereby incorporated by reference in their entireties.

Antibodies of the present invention may be described or specified in terms of the epitope(s) or epitope-bearing portion(s) of a polypeptide of the present invention, which are recognized or specifically bound by the antibody. The antibodies may specifically bind a complete protein encoded by a nucleic acid of the present invention, or a fragment thereof. Therefore, the epitope(s) or epitope bearing polypeptide portion(s) may be specified as described herein, *e.g.*, by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or otherwise described herein (including the sequence listing). Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded as individual species. Therefore, the present invention includes antibodies that specifically bind specified polypeptides of the present invention, and allows for the exclusion of the same.

Thus, another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a polypeptide of the present invention. In one aspect of this embodiment, the antibody is capable of binding to a linear epitope-containing polypeptide comprising at least 6 consecutive amino acids, preferably at least 8 to 10 consecutive amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 consecutive amino acids of a polypeptides of the present invention. In another aspect of this embodiment, the antibody is capable of binding to a nonlinear epitope-containing polypeptide comprising 10 amino acids in length, further preferably 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, or 100 amino acids, further preferably, a contiguous surface of the native conformation of a polypeptide of the present application. Additionally, the antibody is capable of binding a nonlinear epitope presented by a synthetic peptide designed to mimic a contiguous surface of the native conformation of a polypeptide of a sequence selected from the group consisting of GENSET polypeptides. Antibodies that bind linear epitopes may be used in combination with antibodies that bind nonlinear epitopes for instance, in assays that detect proper protein folding.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not specifically bind any other analog, ortholog, or homologue of the polypeptides of the present invention are included. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein, e.g., using FASTDB and the parameters set forth herein) to a polypeptide of the present invention are also included in the present invention. Further included in the present invention are antibodies, which only bind polypeptides encoded by polynucleotides, which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be

mRNA (Malone, et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example,N[1-2,3-dioleyloxy)propyll-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island,N.Y. (See, also, Feigner, et al., Proc. Nad Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Similarly, anionic and neutral liposomes are readily available, such as from AvantiPolar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art (Straubinger, et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference). For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated (U.S. Patent 5,965,421, which disclosure is hereby incorporated by reference).
Generally, the ratio of DNA to liposomes will be from about 10: 1 to about 1: 10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ratio will be about 3: 1 to about 1: 3. Still more preferably, the ratio will be about 1: 1. Additionally, liposomes may be targeted to specific cell types by embedding a targeting moiety such as a member of a receptor- receptor ligand pair into the lipid envelope of the vesicle. Useful targeting moieties specifically bind cell surface ligands, for example, CD48 or the SCF receptor on mast cells. Thus, anti-CD48 antibodies or SCF ligand are examples of useful mast cell-targeting moieties (U.S. Patent 6177433, U.S. Patent 6110490, and P.C.T No. WO9704748, which disclosures are hereby incorporated by reference in their entireties).

In a further embodiment, the polynucleotide of the invention may be entrapped in a liposome [Ghosh and Bacchawat, (1991), Targeting of liposomes to hepatocytes, IN: Liver

In an embodiment, Armapoptin polynucleotides are used in a method of gene therapies to restore cell-cell adhesion and to promote caspase-dependent apoptosis, preferably in epithelial cell-based tumors including breast carcinoma, ovarian carcinoma, lung carcinoma, non-small cell lung carcinoma (NSCLC), and squamous cell carcinoma of head and neck (SCCHN). Preferred compositions of Armapoptin to be used in methods of gene therapy, further referred to as "gene therapy compositions of Armapoptin" are compositions comprising the full-length DNA, SEQ ID NO:29, or fragments thereof, encoding a polypeptide or fragments thereof, including the sequences

aatcctagtcttcgtttggtccggttgcactcttcctatagcccagagggcgagagggcctgtggcctgggggaaggaggacgaggttctgcct
ggatcccagcaggacgctgtgccatttgggaacaaaggaatagtctgcctggaatccctgcagatcttggggccggaggccagtccaaccct
tggagcaggaagaaacgcaaagttgtcaagaaccaagtcgagctgcctcagagccggcccgcagtagctgcagactccgcccgcgacgtg
tgcgcgcttctctgggccagagcgagcctgttttgtgctcgggttaagagatttgtcccagctataccgcgtggccgctggtgtggttatcgggg
ctggtgcctgctactgtgtatacagactggcttggggaagagacgagaacgagaaaatctgggacgaagacgaggagtctacggacacctc
akagattggggttgagactgtgaaaggagctaaaactaacgctggggcagggtctggggccaaacttcagggtgattcagaggtcaagcctg
aggtgagtttgggactcgaggattgtccgggtgtaaaagagaaggcccattcaggatcccacagcggaggtggcctagaggccaaggccaa
ggccctttcaacacgctgaaggaacaggcaagtgcaaaggcaggcaaaggggctagggtgggtaccatctctgggaacaggacccttgca
ccgagtttaccctgcccaggaggcaggggtggaggctgccaccccaccaggagtggatctagggccgggggcagggcaagtggaaaatc
caagggaaaggcccgaagtaagagcaccagggctccagctacaacatggcctgtccggagaggcaagttcaactttccttataaaattgatga
tattctgagtgctcccgacctccaaaaggtcctcaacatcctggagcgaacaaatgatccttttattcaagaagtagccttggtcactctgggtaac
aatgcagcatattcatttaaccagaatgccatacgtgaattgggtggtgtcccaattattgcaaaaaaaaaaaaaaaa,

or

tctgagtacc agctccccac tgccctgagg gcgggccggc ctgcggcgga gggaaaaaggaagaggagaa ggaaattgtc
ccgaatccct gcagtgggtc caagcctctc ccgggtggccagtctttctg taggttgcgg cacaacgcca ggcaaaagaa
gaggaaggaa tttaatcctaatcggtggag gtcgatttga gggtctgctg tagcaggtgg ctccgcttga agcgagggaggaagtttcct
ccgatcagta gagattggaa agattgttgg gagtggcacaccactagggaaaagaagaag gggcgaactg cttgtcttga
ggaggtcaac ccccacaatc agctcttgtggccttgaagt ggctgaagac gatcaccctc cacaggcttg agcccagtcc
cacagccttcctcccccagc ctgagtgact actctattcc ttggtccctg ctattgtcgg ggacgattgcatgggctacg ccaggaaagt
aggctgggtg accgcaggcc tggtgattgg ggctggcgcctgctattgca tttatagact gactagggga agaaaacaga
acaaggaaaa aatggctgagggtggatctg gggatgtgga tgatgctggg gactgttctg gggccaggta
taatgactggtctgatgatg atgatgacag caatgagagc aagagtatag tatggtaccc accttgggctcggattggga ctgaagctgg
aaccagagct agggccaggg caagggccag ggctacccgggcacgtcggg ctgtccagaa acgggcttcc cccaattcag
atgataccgt tttgtcccctcaagagctac aaaaggttct ttgcttggtt gagatgtctg aaaagcctta tattcttgaagcagctttaa
ttgctctggg taacaatgct gcttatgcat ttaacagaga tattattcgtgatctgggtg gtctcccaat tgtcgcaaag attctcaata
ctcgggatcc catagttaaggaaaaggctt taattgtcct gaataacttg agtgtgaatg ctgaaaatca gcgcaggcttaaagtataca
tgaatcaagt gtgtgatgac acaatcactt ctcgcttgaa ctcatctgtgcagcttgctg gactgagatt gcttacaaat atgactgtta
ctaatgagta tcagcacatgcttgctaatt ccatttctga ctttttcgt ttattttcag cgggaaatga agaaaccaaacttcaggttc
tgaaactcct tttgaatttg gctgaaaatc cagccatgac tagggaactgctcagggccc aagtaccatc ttcactgggc tccctcttta
ataagaaaga gaacaaagaagttattctta aacttctggt catatttgag aacataaatg ataatttcaa atgggaagaaaatgaaccta

ctcagaatca attcggtgaa ggttcacttt ttttcttttt aaaagaatttcaagtgtgtg ctgataaggt tctgggaata gaaagtcacc atgatttttt ggtgaaagtaaaagttggaa aattcatggc caaacttgct gaacatatgt tcccaaagag ccaggaataacaccttgatt ttgtaattta gaagcaacac acattgtaaa ctattcattt tctccaccttgtttatatgg taaaggaatc ctttcagctg ccagttttga ataatgaata tcatattgtatcatcaatgc tgatatttaa ctgagttggt ctttaggttt aagatggata aatgaatatcactacttgtt ctgaaaacat gtttgttgct ttttatctcg ctgcctagat tgaaatattttgctatttct tctgcataag tgacagtgaa ccaattcatc atgagtaagc tcccttctgtcattttcatt gatttaattt gtgtatcatc aataaaattg tatgttaatg ctggaagggaaaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa.

Further preferred are compositions comprising PCR-based subcloning of the gene therapy compositions of Armapoptin into plasmid vectors such as pCMVβ or pSVβ, tissue-specific promoter-containing plasmids such as the MUC1 promoter, which allows epithelial cell specific expression and is up-regulated during malignancy, and the P450arom promoter II for breast carcinomas employing liposomal delivery systems by methods described in Patel, US Patent 6,225,090, 2001, Thierry, US Patent 6,110,490, 2000; Wolff, et al., US Patent 6,228,844, 2001, Graham, et al., Int.J.Cancer 92:382-387, 2001, Zhou, et al, Cancer Res. 61:2328-2334, 2001, which disclosures are hereby incorporated in their entireties. Further preferred are compositions comprising polynucleotides of the invention cloned into adenoviral vectors (Beach, et al., US Patents 5,968,821, 1999, and 6,211,334, 2001; Mehtali, et al., US Patent 6,204,060, 2001), and MoMLV-based retroviral vectors for gene delivery into dividing cells, i.e. tumor tissues according to methods described by Holt, et al., US Patent 6,177,410, 2001, which disclosures are hereby incorporated in their entirety.

Methods to deliver preferred compositions of Armapoptin polynucleotides and fragments thereof, comprise local injection of preferred compositions of the invention into tumor tissue or surrounding vessels, or ex vivo therapy. Further methods comprise tumor tissue specific targeting of Armapoptin polynucleotides or fragments thereof in a plasmid via antibodies or other ligands, which recognize tumor-specific receptors. These ligands will be covalently linked to polycations such as poly-L-lysine or liposomes, and complexed with preferred gene therapy compositions of Armapoptin. Preferred tumor cell types to be used in methods of gene therapy include breast carcinoma, cervix adenocarcinoma, ovarian carcinoma, lung carcinoma, and squamous cell carcinoma of head and neck derived from mammalian cells including rodent and human. Assessment of therapeutic efficacies will include tumor regression following delivery of preferred gene therapy compositions of Armapoptin as monitored by measurement of tumor circumference. Apoptosis will be measured by morphological assessments including retraction of cytoplasmic extension, cell rounding and detachment, and via MTT assays, which measure mitochondrial function for viability, cell death and caspase activity, and DNA fragmentation analysis as described by Noteborn, et al. US Patent 5,981,502, 1999; Boone, et al., J.Biol.Chem. 275:37596-37603, 2000; Shibata, et al., Cancer Gene Therapy. 8:23-35, 2001; Lacour, et al., Cancer Research 61:1645-1651, 2001), which disclosures are hereby incorporated by reference in their entireties.

proteoglycans on cell surfaces. Similarly, adenoviral vectors are effectively targeted for the treatment of systemic and local disease using the ability of FGF family polypeptides to bind their cognate FGFR's with high affinity (Sosnowski, *et al.*, Curr Opin Mol Ther 1: 573-579, 1999, which disclosures are hereby incorporated by reference in their entirety). As a further embodiment of this invention is a method of retargeting a FGF-22 polypeptide or chimeric polypeptide encoded as part of an adenoviral or AAV delivery system to cells expressing cognate FGFR complexes using the methods of Hoganson, *et al.*, (Mol Ther 3: 105-112, 2001) and Qing, *et al.* (Nat Med 5: 71-77, 1999), which disclosures are hereby incorporated by reference in their entirety. Preferably the FGF-22 polypeptide is expressed, in part or in whole, with the viral delivery system as a bifunctional conjugate consisting of a blocking anti-adenoviral knob Fab fragment linked to FGF-22 using the methods of Goldman, *et al.* (Cancer Res 57:1447-51, 1997) and Doukas, *et al.* (FASEB J 13:1459-66, 1999). Preferably the FGFR complex is the FGFR-1 polypeptide or FGFR-1 polypeptide ligand binding moiety.

Protein of SEQ ID NO:18 (Internal designation Clone 229633_253-2-5-2-A11-F)

The cDNA of Clone 229633_253-2-5-2-A11-F (SEQ ID NO:17) encodes the STAM-SAPper (STAMSAP) protein comprising the amino acid sequence: MDRALQVLQSIDPTDSKPDSQDLLDLEDICQQMGPMIDEKLEEIDRKHSELSELNVKVLEA LELYNKLVNEAPVYSVYSKLHPPAHYPPASSGVPMQTYPVQSHGGNYMGQSIHQVTVAQ SYSLGPDQIGPLRSLPPNVNSSVTAQPAQTSYLSTGQDTVSNPTYMNQNSNLQSATGTTAY TQQMGMSVDMSSYQNTTSNLPQLAGFPVTVPAHPVAQQHTNYHQQPLL (SEQ ID NO:18). Accordingly, it will be appreciated that all characteristics and uses of the polypeptides of SEQ ID NO:18 described throughout the present application also pertain to the polypeptides encoded by the nucleic acids included in Clone 229633_253-2-5-2-A11-F. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NO:17 described throughout the present application also pertain to the nucleic acids included in Clone 229633_253-2-5-2-A11-F. A preferred embodiment of the invention is directed toward the compositions comprising SEQ ID NO:17, SEQ ID NO:18, and Clone 229633_253-2-5-2-A11-F. Another preferred embodiment of the invention is directed toward compositions comprising polynucleotide fragments of at least eighteen contiguous nucleotides selected from: gagcaagacgtggtgatgccaattggtggaaaggagaaaatcac, preferably those polynucleotides that encode for polypeptides having a biological activity described herein. Further preferred polynucleotides of the present invention include nucleic acids comprising: gaagcggmgsggtctagggagccgcggccgcgggtcacccggcgggtagcagttgctgagtgtcagctagacagcagcgactagggct cgggcgccggcgagatgcctttgttcaccgccaacccccttcgagcaagacgtggtgatgccaattggtggaaaggagaaaatcac preferably those that encode for polypeptides having a biological activity described herein. Further preferred polynucleotides of the present invention include nucleic acids of SEQ ID NO:17 comprising

example, high, constitutive expression from the CMV promoter or regulated expression from a tetracycline-repressible promoter, both of which are readily commercially available). Said polynucleotides are delivered to cells in vitro or in situ by methods common to the art such as electroporation, calcium phosphate transfection, or adenoviral transduction [Maniatis, T., et al. Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (1982) and Cheng, S., et al. (2001) Calcif. Tissue Int. 68:87-94, which disclosures are hereby incorporated by reference in their entireties]. Cells are introduced to a site of desired bone growth in vitro, in situ, or in vivo by methods comprising injection, introduction through a catheter, or surgical implantation of a cell-containing stent, for example, on an osteopenic bone (U.S. Patent 6034062 and U.S. Patent 6206914, which disclosures are hereby incorporated by reference in their entireties).

COVI is associated with vascular smooth muscle cells (VSMC) in the ECM. The COVI splice variant has enhanced ability to promote vascular matrix remodeling, i.e., formation of new vessels (e.g., during development or tissue expansion), and healing of damaged vessels such as those resulting from injury, incision, burns, disease, cardiac infarction, ulcers, diabetic ulcers, and chronic conditions such as atherosclerosis. A preferred embodiment of the invention is a method to promote vascular remodeling by contacting a vascular remodeling-stimulating amount of COVI polypeptide with cells. Preferred cells include but are not limited to VSMC, vascular epithelial cells, and fibroblasts. Further preferred cells include but are not limited to human VSMC, vascular epithelial cells, and fibroblasts in intact tissue (i.e., in a milieu of ECM proteins such as collagen). COVI polypeptides are delivered to cells in physiologically acceptable solution, for example, pH-buffered saline or viscous solutions such as those including glycerol or dextrose. Said solution may be applied topically to surface wound tissue in the treatment of ulcers, lesions, injuries, diabetic ulcers, burns, trauma, stasis ulcers, periodontal conditions, lacerations, and other conditions. In addition, intraperitoneal wound tissue such as that resulting from invasive surgery may be treated with a physiologically acceptable solution comprising COVI polypeptides to accelerate vascular remodeling. For example, the surgical plane may be coated with said solution prior to closing the surgical site to facilitate internal capillary perfusion and healing. In addition, the rate of localized healing may be increased by the subdermal administration of said solution by methods common to the art such as injection (U.S. Patent 6,096,709, which disclosure is hereby incorporated by reference in its entirety).

Timely vascular remodeling is an urgent factor in the case of cardiac infarction to prevent enlargement of the organ. A further preferred embodiment of the invention is a method of contacting a vascular remodeling-stimulating amount of COVI polypeptide with cells. The method comprises the step of contacting COVI polypeptides with cells by implantation of a COVI polypeptide-releasing stent, for example surgically or via catheter (U.S. Patent 5,500,013 and U.S. Patent 5,449,382, which disclosures are hereby incorporated by reference in their entireties). Preferred cells include but are not limited to those found in cardiac tissue damaged as a result of

infarction or within vessels for treating various problems such as atherosclerosis, stenonses, strictures, or aneurysms to reinforce collapsing, partially occluded, or weakened sections.

A further preferred embodiment of the invention is a method to promote vascular remodeling by delivering polynucleotides encoding COVI polypeptides to cells. This method is directed toward purposes such as transplantation of cells expressing COVI polypeptides. Preferred cells include but are not limited to VSMC, vascular epithelial cells, and fibroblasts. Further preferred cells include but are not limited to human VSMC, vascular epithelial cells, and fibroblasts, preferably in intact tissue (i.e., in a milieu of ECM proteins such as collagen). Preferred polynucleotides comprise polynucleotides encoding COVI polypeptides operably linked to an expression control unit (e.g., a promoter) that will deliver a vascular remodeling-stimulating amount of COVI expression (for example, high, constitutive expression from the CMV promoter or regulated expression from a tetracycline-repressible promoter, both of which are readily commercially available). Said polynucleotides are delivered to cells in vitro or in situ by methods common to the art such as electroporation, calcium phosphate transfection, or adenoviral transduction [Maniatis, T., et al., Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (1982) and Cheng, S., et al. (2001) Calcif. Tissue Int. 68:87-94, which disclosures are hereby incorporated by reference in their entireties]. Further included in the method is a step of delivering said cells to a desired site of vascular remodeling (including but not limited to wounds, incisions, injuries, ulcers, and diseased or otherwise hypovascular lesions) by methods common to the art such as injection or catheter delivery of cell suspensions or surgical implantation of intact tissue endoscopically or invasively (U.S. Patent 5,669,925 and U.S. Patent 5,683,345, which disclosures are hereby incorporated by reference in their entireties).

COVI polypeptide is also present as a highly modified keratan sulfate proteoglycan (KSPG) in the cornea. KSPG's are associated with ECM proteins in the cornea and function to maintain corneal shape and opacity. In a further embodiment of the invention, a cornea-maintaining effective amount of COVI polypeptide is used in a method for maintaining a desired shape (e.g., following laser surgery or non-invasive orthokeratological procedures) or opacity of corneal tissues (e.g., at the onset of cataract formation). This method comprises the step of contacting COVI polypeptides with the ECM of the cornea in a physiologically acceptable solution. A preferred physiologically acceptably solution includes pH-buffered saline. Preferred method of contact is by an eye-drop mechanism (P.C.T. 00119386, which disclosure is hereby incorporated by reference in its entirety).

Protein of SEQ ID NO:4 (Internal designation Clone 1000848582_181-40-4-0-A11-F)

The cDNA of clone 1000848582_181-40-4-0-A11-F (SEQ ID NO:3) encodes the protein of SEQ ID NO:4 comprising the amino acid sequence

MELALRRSPVPRWLLLLPLLLGLNAGAVIDWPTEEGKEVWDYVTVRKDAYMFWWLYY
ATNSCKNFSELPLVMWLQGGPGGSSTGFGNFEEIGPLDSDLKPRKTTWLQAASLLFVDNP
VGTGFSYVNGSGAYAKDLAMVASDMMVLLKTFFSCHKEFQTVPFYIFSESYGGKMAAGI

detecting protease levels in a test solution or to screening for molecules that interact with SSSPI as discussed in the following embodiment. In another embodiment of the invention, binding complexes of SSSPI polypeptide and the aforementioned test agents are used in a method to screen for compounds that inhibit interaction of SSSPI polypeptide with serine protease substrates. This method comprises the steps: i) allowing SSSPI polypeptide-test agent binding complex to form; ii) adding SSSPI substrate (such as elastase); iii) measuring SSSPI binding to substrate directly or indirectly by methods common in the art (e.g., fluorescent labeling of the substrate molecule or of an antibody against said substrate). This method is applied, for example, to screening for molecules that inhibit SSSPI biological activity.

In a preferred embodiment of the invention, a method of inhibiting protein degradation with a biologically active SSSPI polypeptide or a polynucleotide construct comprising polynucleotides encoding said polypeptide is provided. This method comprises the step of contacting a protein degradation-inhibiting effective amount of SSSPI polypeptide with proteins in a solution of appropriate pH and salt concentration to allow SSSPI biological activity (e.g., buffered saline). In an additional embodiment, SSSPI polypeptide is combined with other protease inhibitors and used in a method to inhibit protein degradation. This method comprises the steps: combining a protein degradation-inhibiting effective amount of SSSPI polypeptide with effective amounts of other protease inhibitors to form a protease inhibitor cocktail and contacting said cocktail with proteins in a solution of appropriate pH and salt concentration to allow SSSPI biological activity. Preferred protease inhibitors are of a different specificity than SSSPI to maximize the protease-inhibiting effectiveness of the cocktail, such as Kunitz-, trypsin inhibitor-like cystine-rich domain (TIL)-, thyroglobulin-, Kazal-, and netrin (NTR)- type protease inhibitors.

Biologically acceptable salts of the SSSPI polypeptide also fall within the scope of the invention. The term "biologically acceptable salts" as used herein means an inorganic acid addition salt such as hydrochloride, sulfate, and phosphate, or an organic acid addition salt such as acetate, maleate, fumarate, tartrate, and citrate. Examples of biologically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of biologically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of biologically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine.

Compounds provided herein can be formulated into "physiologically acceptable compositions" by admixture with physiologically acceptable nontoxic excipients and carriers. Such compositions may be prepared for use in parenteral administration, particularly in the form of liquid solutions or suspensions; oral administration, particularly in the form of tablets or capsules; intranasally, particularly in the form of powders, nasal drops, or aerosols; dermally, via, for example, transdermal patches; or prepared in other suitable fashions for these and other forms of administration as will be apparent to those skilled in the art.

4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue. Therapies may be designed to utilize RET-A-MODULIN cytotoxic properties. In particular, therapies to enhance RET-A-MODULIN expression or administration of said polypeptides are useful in promoting inhibition or death of cancerous cells. Cytotoxic reagents may include, without limitation, full length or fragment RET-A-MODULIN polypeptides, mRNA, or any compound, which increases RET-A-MODULIN biological activity.

Another therapeutic approach within the invention involves administration of RET-A-MODULIN therapeutic compositions (polynucleodtide, antibody, small molecule agonist or recombinant RET-A-MODULIN polypeptide), either directly to the site of a desired target cell or tissue (for example, by injection) or to a site where the composition will be further directed to the target cell or tissue, or systemically (for example, by any conventional recombinant protein administration technique). The dosage of RET-A-MODULIN depends on a number of factors, including the size and health of the individual patient, but, generally, between 0.1 mg and 100 mg inclusive is administered per day to an adult in any physiologically acceptable formulation.

In another embodiment, RET-A-MODULIN polypeptides and nucleic acid sequences find diagnostic use in the detection or monitoring of conditions involving aberrant levels of apoptosis. For example, decreased expression of RET-A-MODULIN may be correlated with decreased apoptosis in humans. Accordingly, a decrease or increase in the level of RET-A-MODULIN production may provide an indication of a deleterious condition. Levels of RET-A-MODULIN expression may be assayed by any standard technique such as Northern blot analysis and RT-PCR in biopsy specimen.

These embodiments comprise methods for detection of RET-A-MODULIN-mediated proliferation inhibition and apoptosis including *in vitro* activity tests of RET-A-MODULIN or other proteins of the invention or fragments thereof, further cellular proliferation assays, and cellular apoptosis/necrosis assays. Specific examples of apoptosis assays are also provided in the following references. Assays for apoptosis in lymphocytes are disclosed by Noteborn et al., US Patent 5,981,502, 1999, Li *et al.*, "Induction of apoptosis in uninfected lymphocytes by HIV-1 Tat protein", Science 268: 429-431, 1995; Gibellini *et al.*, "Tat-expressing Jurkat cells show an increased resistance to different apoptotic stimuli, including acute human immunodeficiency virus-type 1 (HIV-1) infection", Br. J. Haematol. 89: 24-33, 1995; Martin *et al.*, "HIV-1 infection of human CD4.sup.+ T cells *in vitro*. Differential induction of apoptosis in these cells." J. Immunol. 152:330-342, 1994; Terai *et al.*, "Apoptosis as a mechanism of cell death in cultured T lymphoblasts acutely infected with HIV-1", J. Clin Invest. 87: 1710-1715, 199 1; Dhein *et al.*, "Autocrine T-cell suicide mediated by APO-1/(Fas/CD95)", Nature 373: 438-441, 1995; Katsikis *et al.*, "Fas antigen stimulation induces marked apoptosis of T lymphocytes in human

throughout the present application also pertain to the polypeptides encoded by the nucleic acids included in Clone 1000855165_205-99-1-0-A5-F. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NO:47 described throughout the present application also pertain to the nucleic acids included in Clone 1000855165_205-99-1-0-A5-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:47, SEQ ID NO:48, and Clone 1000855165_205-99-1-0-A5-F. Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

The cDNA of clone 500721700_204-43-4-0-H10-F (SEQ ID:51) encodes the protein of SEQ ID NO:52 comprising the amino acid sequence:
MIYTMKKVHALWASVCLLLNLAPAPLNADSEEDEEHTIITDTELPPLKLMHSFCAFKSDD
GPCKAIMKRFFFNIFTRQCEEFIYGGCEGNQNRFESLEECKKMCTREKPDFCFLEEDPGICR
GYITRYFYNNQTKQCERFKYGGCLGNMNNFETLEECKNICEDGPNGXQVDNYGTQLNAV
NNSLTPQSTKVPSLFEFHGPSWCLTPADRGLCRANENRFYYNSVIGKCRPFKYSGCGGNE
NNFTSKQECLRACKKGFIQRISKGGLIKTKRKRKKQRVKIAYEEIFVKNM. Accordingly, it will be appreciated that all characteristics and uses of polypeptides of SEQ ID NO:52 described throughout the present application also pertain to the polypeptides encoded by the nucleic acids included in Clone 500721700_204-43-4-0-H10-F. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NO:51 described throughout the present application also pertain to the nucleic acids included in Clone 500721700_204-43-4-0-H10-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:51, SEQ ID NO:52, and Clone 500721700_204-43-4-0-H10-F. Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

The protein of SEQ ID NO:48 encodes Tifapinix. The protein of SEQ ID NO:52 encodes Tifapinix-A58S. Tifapinix-A58S differs from Tifapinix in having serine at position 58 rather than alanine (A58S) (numbered from the initiating methionine of Tifapinix). It will be appreciated that the specification, composition, and embodiments directed herein to Tifapinix also are given to be directed as well to Tifapinix-A58S. Furthermore, it will also be appreciated that in said specification, composition, and embodiments directed to any polypeptide of Tifapinix wherein said polypeptide includes alanine at position 58, that said specification, composition, and embodiments given to be directed as well to the corresponding polypeptide of Tifapinix include amino acid serine at position 58.

Tifapinix is a novel splice variant of tissue factor pathway inhibitor (TFPI-1). Tissue factor (TF) initiates the extrinsic coagulation pathway (US Patent 5,849,875; US Patent 5,106,833; US Patent 6,103,499; US Patent 5,773,251; US Patent 5,994,125, 1999, which disclosures are hereby incorporated by reference in their entirety). TFPI-1 is also known as lipoprotein associated

coagulation inhibitor (LACI), so named because of its affinity for plasma lipoprotein.

Tifapinix has novel function as described below.

TFPI-1 is a secreted trivalent Kunitz-type plasma proteinase inhibitor that negatively regulates the initiation of coagulation by producing activated factor X (FXa) feedback inhibition of the catalytic complex of activated factor VII (FVIIa) and TF. The second Kunitz domain of TFPI-1 binds and inhibits FXa, whereas the first Kunitz domain is responsible for the inhibition of FVIIa in the TF-FVIIa complex. The linker region between Kunitz domains 1 and 2 of TFPI-1 is comprised of 20 amino acids (US Patent 5,849,875 which disclosures is hereby incorporated by reference in its entirety): TRDNANRIIKTTLQQEKPDF. The function of the third Kunitz domain is unknown, although there is evidence that it contains a heparin binding site. Heparin binding site(s) have also been mapped carboxyl-terminal to the third Kunitz domain.

TFPI-1 directly inhibits FXa and, in a FXa-dependent fashion, produces feedback inhibition of the TF-FVIIa catalytic complex. TFPI-1 is the major inhibitor of the protease activity of the TF-FVIIa complex. The allosteric promotion of TF-FVIIa binding by Kunitz domain 1 on FXa binding to Kunitz domain 2 presumably is carried out at least in part through the linker region between Kunitz domains 1 and 2. The finding that the Kunitz domain 2, which binds FXa, is required for inhibition of the TF-VIIa complex has led to the proposal that TFPI-1 inhibits TF-FVIIa by forming a quaternary TF-FVIIa-FXa-TFPI-1 complex. The formation of a quaternary complex can result from either the initial binding of TFPI-1 to FXa, with subsequent binding to the TF-VIIa complex or, alternatively, TFPI-1 could bind directly to a preformed TF-FVIIa-FXa comples. The consequence of the formation of the quaternary complex is that TF can no longer participate in initiating coagulation.

Aside from it role in coagulation, FXa plays a role in inflammation. FXa generated by TF-FVIIa has been shown to lead to pro-inflammatory activation of vascular endothelial cells through its cleavage of protease-activated receptor 2 (PAR2) (Camerer, E et al., Proc. Natl. Acad. Sci. USA 97:5255-60 (2000) which disclosure is hereby incorporated by reference in its entirety). FXa can also elicit a pro-inflammatory cellular response by cleavage of protease-activated receptor 1 (PAR1) (Kravchenko, RM Blood 97:3109-16 (2001) which disclosure is hereby incorporated by reference in its entirety). HLA-DR-restricted macrophage expression of TF in rheumatoid synovium is believed to play a role in disease pathogenesis in part through generation of FXa (Dialynas DP et al., Arthritis and Rheumatism 41:1515-6 (1998) which disclosure is hereby incorporated by reference in its entirety).

TF is a bifunctional molecule capable of inducing both fibrin deposition and angiogenesis in cancer. Cancer patients are prone to venous thromboembolism, and this hypercoagulability favors tumor growth and metastasis. In human lung cancer, melanoma, and breast cancer, TF and vascular endothelial growth factor (VEGF) co-localize in tumor cells; a close correlation exists between TF and VEGF synthesis in tumor cell lines and with angiogenesis in vivo in a severe,

combined immunodeficient mouse model (Rickles, FR et al., Int. J. Hematol. 73:145-50 (2001); Wojtukiewicz MZ et al., Thromb. Haemost. 82:1659-62 (1999); Abdulkadir SA, et al., Hum. Pathol. 31:443-7 (2000); Koomagi R et al., Int. J. Cancer 79:19-22 (1998) which disclosures are hereby incorporated by reference in their entirety).

TF supports metastasis (Mueller BM et al., J. Clin. Invest. 101:1372-8 (1998); Fischer EG et al., J. Clin. Invest. 104:1213-21 (1999) which disclosures are hereby incorporated by reference in their entirety). Equally important for this process are (a) interactions of the TF cytoplasmic domain, which binds the mobility-enhancing actin-binding protein 280, and (b) formation of a proteolytically active TF-FVIIa complex on the tumor cell surface. In primary bladder carcinoma cells, this complex localizes to the invasive edge, in proximity to tumor-infiltrating vessels that stain intensely for TFPI-1. Tumor cell adhesion and migration was shown in vitro to be supported by interaction of TF-FVIIa with TFPI-1 immobilized heparin.

TF antigen has been detected in all cellular elements comprising the atheriosclerotic plaque. The most abundant sources of TF appear to be the macrophages and intimal smooth muscle cells located in the cap surrounding the lipid-rich necrotic core. TF antigen is also present in the medial and endothelial cells overlying the plaque. In addition to its association with vascular cells, TF antigen is also found in the extracellular matrix of the intima and in the necrotic core. This TF may come in contact with circulating blood when the plaque ruptures—the most important precipitant of acute arterial thrombosis (Taubman MB et al., Thrombosis and Haemostasis 82:801-5 (1999) which disclosure is hereby incorporated by reference in its entirety).

Recently it has been shown that TFPI-1 inhibits the proliferation of basic fibroblast growth factor-stimulated endothelial cells. A truncated form of TFPI-1, containing only the first two Kunitz-type proteinase inhibitor domains, has very little antiproliferative activity, suggesting that the carboxyl-terminal region of TFPI-1 is responsible for this activity (Hembrough, TA et al., J. Biol. Chem. 276:12241-8 (2001) which disclosure is hereby incorporated by reference in its entirely). By virtue of this activity, TFPI-1 is an inhibitor of angiogenesis. Anomalous angiogeneisis plays an important role in a number of pathologies, including cancer, proliferative diabetic retinopathy, and rheumatoid arthritis (Folkman, J, Forum (Geneva) 9(3 Suppl 3):59-62 (1999); Danis, RP et al., Expert Opin. Pharmacother 2:395-407 (2001); Stupack, DG et al., Braz J. Med. Biol. Res. 32:573-81 (1999) which disclosures are hereby incorporated by reference in their entirety).

In the case of Tifapinix, alternative splicing results in the internal deletion of exon 5 comprised of 13 amino acids from the linker region between Kunitz domains 1 and 2 (Girard, TJ et al., J. Biol. Chem. 266:5036-41 (1991) which disclosure is hereby incorporated by reference in its entirety). The A58S amino acid substitution that distinguishes Tifapinix-A58S from Tifapinix, as well as from the canonical TFPI-1 amino acid sequence (NCBI Accession No. P10646 which disclosure is hereby incorporated by reference in its entirety), establishes that the alternative

of competing with plasmin for binding to Tifapinix or fragments thereof. It may be labeled already, or it may be labeled subsequently by specifically binding the label to a moiety differentiating the plasmin analogue from plasmin. The phases are separated, and the labeled plasmin analogue in one phase is quantified. In a "sandwich assay", both an insolubilized plasmin-binding agent (PBA), and a labeled PBA are employed. The plasmin analyte is captured by the insolubilized PBA and is tagged by the labeled PBA, forming a tertiary complex. The reagents may be added to the sample in any order. The PBAs may be the same or different, and only one PBA needs to comprise Tifapinix or fragments thereof according to this invention (the other may be, e.g., an antibody). The amount of labeled PBA in the tertiary complex is directly proportional to the amount of plasmin in the sample. The two embodiments described above are both heterogeneous assays. A homogeneous assay requires only that the label beaffected by the binding of Tifapinix or fragments thereof to plasmin. The plasmin analyte may act as its own label if Tifapinix or fragments thereof are used as a diagnostic reagent. A label may be conjugated, directly or indirectly (e.g., through a labeled anti-Tifapinix antibody), covalently (e.g., with SPDP) or noncovalently, to the plasmin-binding protein, to produce a diagnostic reagent. Similarly, the plasmin-binding protein may be conjugated to a solid phase support to form a solid phase ("capture") diagnostic reagent. Suitable supports include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, and magnetite. The carrier can be soluble to some extent or insoluble for the purposes of this invention. The support material may have any structure so long as the coupled molecule is capable of binding plasmin.

In yet another preferred embodiment, Tifapinix or fragments thereof are used for in vivo diagnostic uses. Tifapinix or fragments thereof, i.e. a Kunitz domain that binds very tightly to plasmin can be used for in vivo imaging. Radiolabeled Tifapinix may be administered to a human or animal subject, typically by injection, e.g., intravenous or arterial other means of administration such as subcutaneous, intramuscular in a quantity sufficient to permit subsequent dynamic and/or static imaging using suitable radio-detecting devices. The dosage is the smallest amount capable of providing a diagnostically effective image, and may be determined by means conventional in the art, using known radio-imaging agents as guides. Typically, the imaging is carried out on the whole body of the subject, or on that portion of the body or organ relevant to the condition or disease under study. The radiolabeled binding protein has accumulated. The amount of radiolabeled binding protein accumulated at a given point in time in relevant target organs can then be quantified. A particularly suitable radio-detecting device is a scintillation camera, such as a. gamma. camera. The detection device in the camera senses and records (and optional digitizes) the radioactive decay. Digitized information can be analyzed in any suitable way, many of which are known in the art. For example, a time-activity analysis can illustrate uptake through clearance of the radiolabeled binding protein by the target organs with time. The radioisotope used should preferably be pharmacologically inert, and the quantities administered should not have substantial

sequential coupling of component amino acids, (ii) production by recombinant DNA techniques in a suitable host cell such as bacterial, insect- or mammalian cells, (iii) removal of undesired sequences from LACI and in coupling of synthetic replacement sequences (US patent 5,994,125, 1999, hereby incorporated in its entirety).

Protein of SEQ ID NO:50 (Internal designation Clone 588098_184-11-4-0-H4-F)

The cDNA of Clone 588098_184-11-4-0-H4-F (SEQ ID NO:49) encodes the protein of SEQ ID NO:50 comprising the amino acid sequence MPSSVSWGILLLAGLCCLVPVSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELLRTLNQ PDSQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDTEEAKKQINDYVEKGT QGKIVDLVKELDRDTVFALVNYIFFKGKWERPFEVKDTEEEDFHVDQVTTVKVPMMKRL GMFNIQHCKKLSSWVLLMKYLGNATAIFFLPDEGKLQHLENELTHDIITKFLENEDRRSAS LHLPKLSITGTYDLKSVLGQLGITKVFSNGADLSGVTEEAPLKLSKAVHKAVLTIDEKGTE AAGAMFLEAIPMSIPPEVKFNKPFVFLMIDXNTKSPLFMGKVVNPTQK. Accordingly it will be appreciated that all characteristics and uses of polypeptides of SEQ ID NO:50 described throughout the present application also pertain to the polypeptides encoded by the nucleic acids included in Clone 588098_184-11-4-0-H4-F. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NO:49 described throughout the present application also pertain to the nucleic acids included in Clone 588098_184-11-4-0-H4-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:49, SEQ ID NO:50, and Clone 588098_184-11-4-0-H4-F. Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

The protein of SEQ ID NO:50 encodes CrypAAT, a splice variant of alpha-1-antitrypsin (antitrypsin) with novel function. In CrypAAT, internal splicing within exon 2 leaves the signal sequence intact but results in an N-terminal deletion of 67 amino acids from the mature protein. This deletion extends from the disordered N-terminus through helix A and into helix B (Stein, PE et al., Nature Structural Biology 2:96-113 (1995) which disclosure is hereby incorporated by reference in its entirety). The Met-Ser active site near the C-terminus is intact.

Antitrypsin is synthesized primarily by hepatocytes and is the most abundant proteinase inhibitor in human plasma. Although it diffuses through all organs, and inhibits a large number of proteases, its primary function is in the lung parenchyma, where it protects alveolar tissue from damage by neutrophil elastase, a serine protease released in the course of an inflammatory response. Elastases are defined by their ability to cleave elastin, the matrix protein that gives tissues the property of elasticity. If left uncontrolled, neutrophil elastase leads to excessive inflammation and progressive emphysema. Individuals with antitrypsin deficiency have at least a 20-fold increase risk of developing emphysema.

Antitrypsin is a member of the serpin (serine protease inhibitor) supergene family. The primary function of most of the serpins is the regulation of proteolytic enzymes under both

ETAMLVCKSESVPPVTDWAWYKITDSEDKALMNGSESRFFVSSSQGLSELHIENLNMEAD PGQYRCNGTSSKGSDQAIITLRVRSHLAALWPFLGIVAEVLVLVTIIFIYEKRRKPEDVLDD DDAGSAPLKSSGQHQNDKGKNVRQRNSS. Accordingly, it will be appreciated that all characteristics and uses of the polypeptide of SEQ ID NO:78 described throughout the present application also pertain to the polypeptide encoded by the nucleic acids included in clone 122421_105-076-4-0-H1-F. In addition, it will be appreciated that all characteristics and uses of the nucleic acid of SEQ ID NO:77 described throughout the present application also pertain to the nucleic acids included in clone 122421_105-076-4-0-H1-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:77, SEQ ID NO:78, and Clone 122421_105-076-4-0-H1-F. Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

The protein of SEQ ID NO:78 (BASI2) is a novel polymorphic variant of human basigin. BASI2 displays a signal peptide (MAAALFVLLGFALLGTHG), and two immunoglobulin (Ig) domains (GSKILLTCSLNDSATEVTGHRWLKGGVVLKEDALPGQKTEFKVDSDDQWGEYSCVF and GETAMLVCKSESVPPVTDWAWYKITDSEDKALMNGSESRFFVSSSQGLSELHIENLNMEA DGQYRCNGTSS). Furthermore, BASI2 displays three N-glycosylation sites (NDSA, NGSE, and NGTS). The arginine at position 166 in basigin is changed to leucine in BASI2. Thus, the polymorphic, nonconservative change present in BASI2 is located in the second Ig domain, which is involved in protein-protein interactions. Such a polymorphic change located in the second Ig domain has never been previously reported. Thus, as a novel polymorphic variant of basigin, BASI2 displays similar biological activities as basigin, but displays enhanced kinetic parameters during protein-protein interactions.

BASI2 is a member of the immunoglobulin superfamily, which includes T cell receptors, neural cell adhesion molecules and major histocompatibility complex antigens. BASI2 is a cell surface transmembrane glycoprotein that is broadly distributed, and expressed at particularly high levels on activated gliomas, on tumor cells, on activated T cells and at the retinal pigment epithelium and neonatal blood–brain barrier. BASI2 is involved in cell-cell interactions, and has a multiplicity of biological roles. Notably, BASI2 stimulates the biosynthesis of various matrix metalloproteinases (MMPs), a group of enzymes involved in the degradation of most of the components of the extracellular matrix. In particular, MMP biosynthesis is crucial in tumor secretion and in immune response. BASI2 plays a role in spermatogenesis and fertilization, in neuronal interactions in the central nervous system and in HIV-1 infection.

An embodiment of the present invention relates to methods of using BASI2 or fragment thereof to stimulate the biosynthesis of metalloproteinases. In a preferred embodiment, metalloproteinases produced by such methods can be used in a "cocktail" of proteases that is able to digest a wide range of proteins without knowing any of the proteins. Such protease cocktails are

100038_105-017-4-0-E4-F, 100523_105-019-1-0-F3-F, and 100545_105-019-2-0-E3-F, respectively. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NOs:83, 85, and 97 described throughout the present application also pertain to the nucleic acids included in Clones 100038_105-017-4-0-E4-F, 100523_105-019-1-0-F3-F, and 100545_105-019-2-0-E3-F, respectively. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:97, SEQ ID NO:98, Clone 100038_105-017-4-0-E4-F, Clone 100523_105-019-1-0-F3-F, and Clone 100545_105-019-2-0-E3-F. Also preferred are fragments having a biological activity described herein and the polynucleotides encoding the fragments. A preferred fragment of the polypeptides of SEQ ID NOs:84 and 86 comprises: MLPPLPSRLGLLLLLLCPAHVGGLWWAVGSPLVMDPTSICRKARRLAGRQAELCQAEPE VVAELARGARLGVRECQFQFRFRRWNCSSHSKAFGRILQQGQCGEGHPARTLPP. A preferred fragment of the polypeptides of SEQ ID NO:98 comprises: MLPPLPSRLGLLLLLLCPAHVGGLWWAVGSPLVMDPTSICRKARRLAGRQAELCQAEPE VVAELARGARLGVRECQFQFRFRRWNCSSHSKAFGRILQQGQCGEGAEVGLLSP. A further preferred fragment of the polypeptide sequences of SEQ ID NOs:84, 86, and 98 comprises: MLPPLPSRLGLLLLLLCPAHVGGLWWAVGSPLVMDPTSICRKARRLAGRQAELCQAEPE VVAELARGARLGVRECQFQFRFRRWNCSSHSKAFGRILQQGQ.

A list of preferred embodiments of the invention follows.

A preferred embodiment is a composition, comprising a SAW-1 polypeptide sequence of SEQ ID NO:84.

A preferred embodiment is a composition, comprising a SAW-1 polypeptide sequence of SEQ ID NO:86.

A preferred embodiment is a composition, comprising a SAW-1 polypeptide fragment having biological activity.

A preferred embodiment is a composition, comprising a SAW-2 polypeptide sequence of SEQ ID NO:98.

A preferred embodiment is a composition, comprising a SAW-2 polypeptide fragment having biological activity.

A preferred embodiment is a composition, comprising a polynucleotide sequence of SEQ ID NO:83 encoding a SAW-1 polypeptide.

A preferred embodiment is a composition, comprising a polynucleotide sequence of SEQ ID NO:85 encoding a SAW-1 polypeptide.

A preferred embodiment is a composition, comprising a polynucleotide sequence encoding a biologically active SAW-1 polypeptide fragment.

A preferred embodiment is a composition, comprising a polynucleotide sequence of SEQ ID NO:97 encoding a SAW-2 polypeptide.

used as an index of the condition, treatment, or effect of substances directly administered to the subject or to which the subject is exposed in the environment. This marker may thus also play a role as prognostic indicators, preferably concerning inflammatory diseases. For example, it can be used in the Alzheimer's disease where chronic inflammation is an accompanying physiological contributor to this multifactor pathology. Also in a preferred embodiment, the present invention provides a method of detecting the presence and/or monitoring the metastatic progress of a malignancy. Indeed, metastatic potential can be influenced by the interaction between the neoplastic cells and their microenvironment such as extracellular matrix and proteolytic enzymes including the present protein. The invention thus includes test kits useful for quantify the amount of the present protein in a biological sample comprising the steps of contacting the biological sample with a specific monoclonal or polyclonal antibody specific for the present protein and coupled to detectable markers. Thus, the condition of a patient can be monitored continuously and the quantified amount of such proteins measured in the pathological sample can be compared with the amount quantified in a biological sample of a normal individual or with the previous analysis of the same patient. In all this embodiment, this marker can be measured effectively in plasma, serum or blood, by any suitable method, including immunoassays. It can also preferably be mesured in tissues and fluids recovered from inflammatory sites. Thus, the condition of a subject can be monitored continuously and the quantified amount of this particular protein measured in the pathological sample can be compared with the amount quantified in a biological sample of a normal individual.

Polynucleotides of SEQ ID NO:93 (Internal designation Clone 150011_110-006-3-0-D5-F) and SEQ ID NO:95 (Internal designation Clone 500737461_205-43-3-0-E3-F)

The cDNA of clone 150011_110-006-3-0-D5-F (SEQ ID:93) encodes an allele of Tissue Factor Pathway Inhibitor-1 (TFPI-1), comprising the nucleotide sequence:

CTCTTTGCTCTAACAGACAGCAGCGACTTTAGGCTGGATAATAGTCAAATTCTTACCTC
GCTCTTTCACTGCTAGTAAGATCAGATTGCGTTTCTTTCAGTTACTCTTCAATCGCCAG
TTTCTTGATCTGCTTCTAAAAGAARAAGTAGAGAAGATAAATCCTGTCTTCAATACCT
GGAAGGAAAAACAAAATAACCTCAACTCCGTTTTGAAAAAAACATTCCAAGAACTTT
CATCAGAGATTTTACTTAGATGATTTACACAATGAAGAAAGTACATGCACTTTGGGCT
TCTGTCCCTGCTGCTTAATCTTGCCCCTGCCCCTCTTAATGCTGATTCTGAGGAAGATG
AAGAACACACAATTATCACAGATACGGAGTTGCCACCACTGAAACTTATGCATTCATT
TTGTGCATTCAAGGCGGATGATAGCCCATGTAAAGCAATCATGAAAAGATTTTTCTTC
AATATTTTCACTCGACAGTGCGAAGAATTTATATATGGGGGATGTGAAGGAAATCAGA
ATCGATTTGAAAGTCTGGAAGAGTGCAAAAAAAATGTGTACAAGAGATAMTGCAAACA
GGATTATAAAGACAACATTGCAACAAGAAAAGCCAGATTTCTGCTTTTTGGAAGAAG
ATCCTGGAATATGTCGAGGTTATATTACCAGGTATTTTTATAACAATCAGACAAAACA
TGTGAACGTTTCAAGTATGGTGGATGCCTGGGCAATATGAACAATTTTGAGACACTGG

AAGAATGCAAGAACATTTGTGAAGATGGTCCGAATGGTTTCCAGGTGGATAATTATGG
AACCCAGCTCAATGCTGTGAATAACTCCCTGACTCCGCAATCAACCAAGGTTCCCAGC
CTTTTTGTTACAAAAGAAGGAACAAATGATGGTTGGAAGAATGCGGCTCATATTTACC
AAGTCTTTYTGAACGCCTTCTGCATTCATGCATCCATGTTCTTTCTAGGATTGGATAGC
ATTTCATGCCTATGTTAATATTTGTGCTTTTGGCATTTCCTTAATATTTATATGTATACG
TGATGCCTTTGATAGCATACTGCTAATAAAGTTTTAATATTTACATGCATAGGAAAAA
AAAAAAAAAA. Accordingly, it will be appreciated that all characteristics and uses of the polypeptides of SEQ ID NO:94 and polynucleotides of SEQ ID NO:93 described throughout the present application also pertain to the nucleic acids included in Clone 150011_110-006-3-0-D5-F. Clone 150011_110-006-3-0-D5-F is alternatively referred to herein as TFPI-C16Pfs in reference to the nucleotide polymorphism that is a subject of the present invention. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:93, SEQ ID NO:94, and Clone 150011_110-006-3-0-D5-F. Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

The cDNA of clone 500737461_205-43-3-0-E3-F (SEQ ID:95) encodes an allele of Tissue Factor Pathway Inhibitor-1 (TFPI-1), comprising the nucleotide sequence:

CTCTTTGCTCTAACAGACAGCAGCGACTTTAGGCTGGATAATAGTCAAATTCTTACCTC
GCTCTTTCACTGCTAGTAAGATCAGATTGCGTTTCTTTCAGTTACTCTTCAATCGCCAG
TTTCTTGATCTGCTTCTAAAAGAAGAAGTAGAGAAGATAAATCCTGTCTTCAATACCT
GGAAGGAAAAACAGAATAACCTCAACTCCGTTTTGAAAAAAACATTCCAAGAACTTT
CATCAGAGATTTTACTTAGATGATTTACACAATGAAGAAAGTACATGCACTTTGGGCT
TCTGTATGCCTGCTGCTTAATCTTGCCCCTGCCCCTCTTAATGCTGATTCTGAGGAAGA
TGAAGAACACACAATTATCACAGATACGGAGTTGCCACCACTGAAACTTATGCATTCA
TTTTGTGCATTCAAGGCGGATGATGGCCCATGTAAAGCAATCATGAAAAGATTTTTCT
TCAATATTTTCACTCGACAGTGCGAAGAATTTATATATGGGGGATGTGAAGGAAATCA
GAATCGATTTGAAAGTCTGGAAGAGTGCAAAAAAATGTGTACAAGAGATAATGCAAA
CAGGATTATAAAGACAACATTGCAACAAGAAAAGCCAGATTTCTGCTTTTTGGAAGA
AGATCCTGGAATATGTCGAGGTTATATTACCAGGTATTTTTATAACAATCAGACAAAA
CAGTGTGAACGTTTCAAGTATGGTGGATGCCTGGGCAATCAACAATTTTGAGACACTG
GAACAATGCAAGAACATTTGTGAAGATGGTCCGAATGGTTTCCAGGTGGATAATTATG
GAACCCAGCTCAATGCTGTGAATAACTCCCTGACTCCGCAATCAACCAAGGTTCCCAG
CCTTTTTGAATTTCACGGTCCCTCATGGTGTCTCACTCCAGCAGACAGAGGATTGTGTC
GTGCCAATGAGAACAGATTCTACTACAATTCAGTCATTGGGAAATGCCGCCCATTTAA
GTACAGTGGATGTGGGGGAAATGAAAACAATTTTACTTCCAAACAAGAATGTCTGAG
GGCATGTAAAAAAGGTTTCATCCAAAGAATATCAAAAGGAGGCCTAATTAAAACCAA
AAGAAAAAGAAAGAAGCAGAGAGTGAAAATAGCATATGAAGAAATTTTTGTTAAAA
ATATGTGAATTTGTTATAGCAATGTAACATTAATTCTACTAAATATTTTATATGAAATG

microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The GENSET polypeptide-encoding cDNAs, or fragments thereof, may also be tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A, the entire contents of which are incorporated by reference. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs. A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the GENSET polypeptide-encoding cDNAs to determine which genes are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of a GENSET polypeptide-encoding gene in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of GENSET gene expression may also be performed using arrays. For example, quantitative analysis of gene expression may be performed with GENSET polynucleotides, or fragments thereof in a complementary DNA microarray as described by Schena *et al.* (1995) Science 270:467-470 and Schena *et al.* (1996), Proc Natl Acad Sci U S A,.93(20):10614-10619 which disclosures are hereby incorporated by reference in their entireties. GENSET polypeptide-encoding cDNAs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C. Cell or tissue mRNA is

Table IV continued...

75	[1-465]	[466-1634]
77	[2-394];[396-564];[681-832]; [1207-1294]	[1-1];[395-395];[565-680]; [833-1206];[1295-1642]
79	[1-218];[220-591];[605-663]	[219-219];[592-604];[664-1466]
81	[1-432]	[433-1406]
83	[1-339]	[340-1754]
85	[1-339]	[340-1754]
87	[1-433];[1261-1355]	[434-1260];[1356-1431]
89	[1-433];[1261-1355]	[434-1260];[1356-1431]
91	[1-738];[884-1342];[1350-1380]	[739-883];[1343-1349];[1381-1417]
93	[1-494];[517-581]	[495-516];[582-1115]
95	[1-189];[191-496];[519-583]	[190-190];[497-518];[584-1307]
97	[1-339]	[340-1855]
99	[1-405];[426-457]	[406-425];[458-667]
101	[1-44];[666-753];[783-813]; [899-965];[981-1013]	[45-665];[754-782];[814-898]; [966-980];[1014-1062]
103	[1-77];[79-412];[418-456];[758-916]	[78-78];[413-417];[457-757];[917-933]
105	[1-287];[289-635]	[288-288];[636-1187]
107	[1-501];[680-719];[721-816]; [822-853];[982-1180]; [1182-1235];[1237-1383]; [1404-1520]	[502-679];[720-720];[817-821]; [854-981];[1181-1181]; [1236-1236];[1384-1403]
109	[1-393];[409-503]	[394-408];[504-1789]
111	[1-777];[779-860];[1365-1408]	[778-778];[861-1364]

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26,
Line 17: "86: 9832-8935" should read -- 86: 9832-9835 --.

Column 35,
Line 63: "omithine" should read -- ornithine --.

Column 38,
Line 38: "osetoprotegerin" should read -- osteoprotegerin --.

Column 40,
Line 22: "268 2984-2988"should read -- 268: 2984-2988 --.

Column 52,
Line 12: "Bateman et." should read --Bateman *et al.* --.

Column 56,
Line 42: "thereof Therefore," should read -- thereof. Therefore, --.

Column 77
Line 25: "ethanolamine" should read -- ethanolarnine --.
Line 32: "ethanolamine" should read -- ethanolarnine --.
Line 47: "ration will" should read -- ratio will --.

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AUG - 7 2006

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 79,
Line 20: "hplc" should read -- HPLC --.

Column 81,
Line 56: "embrionic" should read -- embryonic --.

Column 93,
Line 20: "fragements" should read -- fragments --.

Column 97,
Line 11: "gaccttgca" should read -- gacccttgca --.
Line 24: "gaagttcct" should read -- gaagtttcct --.
Line 28: "ccttcccccagc" should read -- ccttcctcccccagc --.
Line 29: "ggacgttgcat" should read -- ggacgattgcat --.
Line 65: "P450 arom" should read -- P450arom --.

Column 102,
Lines 55-56: "Pat. No. 6,124,008/PCT WO98/46289" should read -- Pat. No. 6,124,008; PCT WO98/46289 --.
Line 62: "acetablular" should read -- acetabular --.

Column 106,
Line 20: "acceptablely acceptable" should read -- acceptable --.

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APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 107,
Line 33: "gccgccggcc" should read -- gccgcggcc --.
Line 35: "gtgtcagtagac" should read -- gtgtcagctagac --.

Column 112,
Line 46: "bums" should read -- burns --.

Column 113,
Line 56: "404-0-A11-F" should read -- 40-4-0-A11-F --.

Column 117,
Lines 39-40: "yeast Candida alibcans" should read -- yeast Candida albicans --.

Column 118,
Line 3: "be reference" should read -- by reference --.
Lines 34-35: "(e) *Bacteriodes fragilis;* (f) *Bacteriodes gracilis;* (g) *Bacteriodes ureolyticus;*" should read -- (e) *Bacteroides fragilis*; (f) *Bacteroides gracilis*; (g) *Bacteroides ureolyticus*; --.

Column 120,
Line 6: "hetertetrameric" should read -- heterotetrameric --.
Line 22: "hyperfinbrinolysis" should read -- hyperbrinolysis --.

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-7 2006

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 124,
Line 47: "trangenic" should read -- transgenic --.

Column 125,
Line 39: "87-93 which" should read -- 87-93) which --.

Column 131,
Line 34: "(o) Pencillin" should read -- (o) Penicillin --.

Column 145,
Lines 38-39: "organic a mine" should read -- organic amine --.

Column 154,
Line 10: "A preferred embodiments" should read --A preferred embodiment --.
Line 49: "anti-oestrogen" should read --anti-estrogen --.

Column 158,
Lines 6-7: "Notebom et al.," should read -- Noteborn et al., --.

Column 159,
Line 2: "matrixproteins" should read -- matrix proteins --.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 160,
Line 38: "500721700_204-434-0-H10-F" should read -- 500721700_204-43-4-0-H10-F --.
Line 42: "500721700_204-434-0-H10-F" should read -- 500721700_204-43-4-0-H10-F --.

Column 161,
Line 28: "by for ming" should read -- by forming --.
Line 33: "comples" should read -- complex --.

Column 162,
Line 45: "266: 503641" should read -- 266: 5036-41 --.

Column 168,
Lines 54-55: "such as a. gamma. camera." should read -- such as a gamma camera. --.

Column 170,
Lines 47-48: "(serine protease inhibitor)" should read -- (serine protease inhibitor) --.

Column 187,
Line 32: "bums" should read -- burns --.

Column 188,
Line 65: "aquous" should read -- aqueous --.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 190,
Line 30: "In other embodiment," should read -- In other embodiments, --.

Column 193,
Line 58: "Contrarily In contrast" should read -- Contrarily, in contrast --.
Line 60: "(Bernot et alet al.," should read -- (Bernot et al., --.

Column 194,
Line 32: "(Li et alet al," should read -- (Li et al., --.

Column 195,
Line 62: "More particularity," should read -- More particularly, --.

Column 197,
Lines 7-8: "347, 83-87" should read -- 347: 83-87 --.

Column 200,
Line 34: "18(2)263-294" should read -- 18(2): 263-294 --.

Column 209,
Line 38: "implicated tumor cell" should read -- implicated in tumor cell --.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

AUG - 7 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 215,
Line 40: "does not contains" should read -- does not contain --.

Column 224,
Line 29: "forma of" should read -- forms of --.
Line 36: "Am J; Med. Genet." should read -- Am. J. Med. Genet. --.

Column 226,
Lines 49-50: "oligonucleotides probes" should read -- oligonucleotide probes --.

Column 228,
Lines 29-30: "deshydrogenase" should read -- dehydrogenase --.
Line 41: "deshydrogenase" should read -- dehydrogenase --.

Column 231,
Line 4: "musculr hypotonia" should read -- muscular hypotonia --.
Line 5: "3-hydrixidicarboxylic" should read -- 3-hydroxydicarboxylic --.
Lines 52-53: "oligonucleotides probes" should read -- oligonucleotide probes --.

Column 232,
Line 13: "122421_105-0764-O-HI-F" should read -- 122421_105-076-4-O-HI-F --.
Line 19: "122421_105-0764-O-HI-F" should read -- 122421_105-076-4-O-HI-F --.

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Saliwanchik, Lloyd & Saliwanchik
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Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 241,
Line 63: "100038_105-0174-0-E4-F," should read -- 100038-105-017-4-0-E4-F, --.
Line 65: "and 100545_105-019-2-E3-F" should read -- and 100545_105-019-2-0-E3-F --.

Column 259,
Line 31: "GATTTCTTC" should read -- GATTTTTCTTC --.

Column 260,
Line 10: "GAAAAAACAT" should read -- GAAAAAAACAT --.
Line 22: "CAAAAAAT" should read -- CAAAAAAAT --.

Column 261,
Line 50: "An recent study" should read -- A recent study --.

Column 263,
Line 18: "In additional preferred embodiment" should read -- In an additional preferred embodiment --.

Column 270,
Line 7: "(swissprot accession numberP02749)" should read -- (swissprot accession number P02749) --.

MAILING ADDRESS OF SENDER:
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Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,989,262

APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

INVENTOR(S) : Stephane Bejanin and Hiroaki Tanaka

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 272,
Line 54: "antiphopholid" should read -- antiphospholid --.
Line 57: "antiphopholid" should read -- antiphospholid --.
Line 59: "antiphopholid" should read -- antiphospholid --.

Column 282,
Lines 10-11: "17beta-hydroxysteroids" should read -- 17 beta-hydroxysteroids --.
Line 15: "17beta-HSD"should read -- 17 beta-HSD --.

Column 289,
Line 21: "0.5MNaCl" should read -- 0.5 M NaCl --.

Column 290,
Line 39: "270: 467470" should read -- 270: 467-470 --.

Column 312,
Line 58: "CH.sub.2" should read -- CH_2 --.
Line 64: "Tne such" should read -- One such --.

Column 313,
Line 41: "0.6-1.2 degree. C." should read -- 0.6-1.2° C. --.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on April 15, 2005.

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Examining Group 1652
Patent Application
Docket No. G-091US05DIV
Serial No. 09/992,095

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Sheridan Swope, Ph.D.
Art Unit	:	1652
Applicants	:	Stephane Bejanin, Hiroaki Tanaka
Serial No.	:	09/992,095
Filed	:	November 13, 2001
Conf. No.	:	1774
For	:	Plasmin Variants and Uses Thereof

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

A Petition and Fee for a two-month Extension of Time through and including April 18, 2005, accompanies this Amendment.

In response to the Office Action dated November 17, 2004, please amend the above-identified patent application as follows:

In the Specification

Please substitute the Title of the invention on page 1, line 1:

~~HUMAN CDNAS AND PROTEINS~~ PLASMIN VARIANTS AND USES THEREOF

Please substitute the following paragraph on page 200, beginning at line 24:

Plasminute is the product of alternative transcription initiation within the plasminogen gene. Transcription initiates within intron N (at least 1036 nucleotides upstream of exon XV) and proceeds through the remainder of the plasminogen gene (Petersen, TE et al., J. Biol. Chem. 265:6104-11 (1990); NCBI Accession No. AL109933.25 which disclosures are hereby incorporated by reference in their entirety). Splicing occurs normally between transcribed exons XV to XIX. Translation initiates within exon XV and is carried out in the plasminogen open reading frame. Plasminute represents the carboxyl-terminal fragment of plasminogen corresponding to amino acids 585 to ~~790~~ 791 (numbered from the amino-terminal glutamic acid residue of secreted plasminogen).

Please substitute the following "Abstract" paragraph on page 394, beginning at line 2:

The invention concerns plasmin variants. Polynucleotides the disclosed plasmin variants are provided. Additionally, methods of using the plasmin polynucleotides and polypeptides are provided herein ~~GENSET polynucleotides and polypeptides. Such GENSET products may be used as reagents in forensic analyses, as chromosome markers, as tissue/cell/organelle-specific markers, and in the production of expression vectors. In addition, they may be used in screening and diagnosis assays for abnormal GENSET expression and/or biological activity and for screening compounds that may be used in the treatment of GENSET-related disorders~~.

In the Claims

1-29 (Canceled).

30. (Currently Amended) A Plasminute polypeptide encoded by ~~the~~ an isolated polynucleotide ~~of claim 29~~ comprising an open reading frame of the human cDNA of deposited clone 789749_182-14-3-0-C12-F.

31. (Currently Amended) A Plasminute ~~polypeptide~~ protease consisting of amino acids 1 to 207 of SEQ ID NO:54~~, or a polypeptide fragment thereof~~.

32-33. (Canceled)

34. (Currently Amended) The ~~polypeptide or polypeptide fragment of claim 33~~ protease of claim 31, wherein said ~~biological activity~~ protease is a serine protease ~~activity~~.

35. (Canceled)

36. (Currently Amended) A composition comprising the ~~polypeptide~~ protease of claim 31 and a physiologically acceptable carrier.

37-52. (Canceled)

53. (New) A composition comprising the polypeptide of claim 34 and a physiologically acceptable carrier.

54. (New) A composition comprising the polypeptide of claim 30 and a physiologically acceptable carrier.

55. (New) A method of digesting a protein comprising contacting a protein with a) a Plasminute polypeptide encoded by an isolated polynucleotide comprising an open reading frame of the human cDNA of deposited clone 789749_182-14-3-0-C12-F; b) a Plasminute protease consisting of amino acids 1 to 207 of SEQ ID NO:54; or c) compositions thereof under conditions that allow for the digestion of said protein.

56. (New) The method of claim 55, wherein a protein is contacted with a Plasminute polypeptide encoded by an isolated polynucleotide ~~comprising~~ an open reading frame of the human cDNA of deposited clone 789749_182-14-3-0-C12-F. changed to "consisting of" by Examiner's Amendment

57. (New) The method of claim 55, wherein a protein is contacted with a Plasminute protease consisting of amino acids 1 to 207 of SEQ ID NO:54.

58. (New) The method of claim 55, wherein a protein is contacted with a composition comprising a carrier and a Plasminute protease consisting of amino acids 1 to 207 of SEQ ID NO:54.

59. (New) The method of claim 55, wherein a protein is contacted with a composition comprising a carrier and a Plasminute polypeptide encoded by an isolated polynucleotide comprising an open reading frame of the human cDNA of deposited clone 789749_182-14-3-0-C12-F.

Remarks

Claims 14-52 are pending in the subject application. Applicants acknowledge that claims 14-29 and 37-52 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have amended claims 30, 31, 34, and 36, canceled claims 14-29, 32, 33, 35, and 37-52, and added new claims 53-59. Support for the amendments and new claim can be found throughout the subject specification and in the claims as originally filed (see, for example, page 202, lines 2-10 and the original claims). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 30, 31, 34, 36, and 53-59 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

By way of the Amendment of this date, Applicants have submitted method of use claims related to the plasminute polypeptide. Applicants acknowledge that the Patent Office may, where appropriate, require applicant, under 35 U.S.C. § 121, to elect claims to either the product or process and that claims directed to the non-elected invention are withdrawn from further consideration under 37 C.F.R. § 1.142. However, Patent Office policy related to the treatment of product and process claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b) indicates that if applicant elects claims directed to the product and the product is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product will be rejoined. With respect to this policy, Applicants respectfully submit that claims 55-59 relate to withdrawn process claims that include all the limitations of, or depend from, the product claims under examination in this matter. Should the product claims currently under examination in this matter be found allowable by the Patent Office, Applicants respectfully request that the Patent Office rejoin claims 55-59 with the currently pending claims and that these claims be allowed as well.

The "Related Applications" section of the subject application is objected to on the grounds the specification fails to claim priority to U.S. application Serial Nos. 60/298,698 and 60/293,574. In addition, the specification is objected to because it does not indicate that the subject application is a divisional of parent application Serial No. 09/924,340. Applicants respectfully assert that the "Related Applications" section of the subject application was amended to correct such issues in their Election Under 35 U.S.C. § 121 dated July 28, 2004 (see page 2 of the amendment/election).

The specification is also objected to because the subject specification (at page 200, lines 30-32) states that plasminute consists of residues 585-790 of plasminogen but SEQ ID NO: 2 consists of residues 585-791 of the plasminogen sequence. Applicants gratefully acknowledge the Examiner's careful review of the subject specification. By this Amendment, Applicants have amended the specification to indicate that the plasminute consists of residues 585-791. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The specification is also objected to because it fails to define the term "GENSET." Applicants respectfully submit that the term relates to the various polypeptides and polynucleotides disclosed within the specification and that definition of the term is not required.

The Examiner has indicated that the title of the invention is not descriptive. Applicants have amended the title of the invention to "Plasmin Variants and Uses Thereof." Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

The Examiner asserts that the oath or declaration submitted in the subject application is defective on the grounds that the filing date for U.S. application Serial No. 60/293,574 is incorrectly listed. Applicants note that an Application Data Sheet was submitted to the Patent Office when the subject application was filed which correctly listed the filing date for U.S. application Serial No. 60/293,574 as May 25, 2001. Therefore, Applicants do not believe it is necessary to provide a newly executed Declaration in view of 37 C.F.R. 1.76(d)(2) which indicates that the Application Data Sheet will govern when the inconsistent information is supplied at the same time by an amendment to the specification, a designation of correspondence address, or a § 1.63 or § 1.67 oath or declaration, except as provided by paragraph (d)(3) of this section. However, if the Examiner maintains this objection in the next Action, Applicants will endeavor to obtain a newly executed Declaration by the inventors. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

The abstract is objected to because the term "GENSET" should be defined and the word "and" should be inserted. As the Abstract has been amended to reflect the currently claimed invention, it is respectfully submitted that this issue is moot. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

The Information Disclosure Statement dated April 26, 2002 is objected to for failing to state the database in which the disclosed sequences for Accession No. AAR34428 and Accession No.

AAR56472, identified as "ab" and "ac", respectively, can be found and that a new "US PTO/1449" is required. Submitted with this Amendment is a new Form PTO/SB/08 (substituted for Form PTO-1449) which provides a complete reference for Accession No. AAR34428 and Accession No. AAR56472. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 30 is objected to for being dependent upon a non-elected claim. Applicants have amended claim 30 to include the limitation of canceled claim 29. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 32 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. However, by this Amendment, claim 32 has been canceled, thereby rendering this rejection moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 31-33 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification and as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully assert that the claims are enabled by the subject specification and that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention. Applicants note that claims 32 and 33 have been canceled, thereby rendering the rejections of those claims moot. The Office Action indicates that the specification is enabled for the polypeptide of SEQ ID NO: 54 but does not provide enablement for any fragment of SEQ ID NO: 54. Applicants note that claim 31 has been amended to delete reference to "or a polypeptide fragment thereof" and that the claim is now directed to a protease rather than a polypeptide. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claim 30 is rejected under 35 U.S.C. § 102(b) as anticipated by Petersen *et al.* (1990) or Castellino *et al.* (1995). In addition, claims 31-36 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Aguzzi *et al.* (2002). The Office Action indicates that the Petersen *et al.* and Castellino *et al.* references teach a polypeptide, human plasminogen, comprising SEQ ID NO: 54. The Office Action further states that

the Aguzzi *et al.* references teaches peptide libraries of human plasminogen fragments linked to beads, displayed on phage, or expressed in host cells. Applicants respectfully traverse.

Applicants respectfully submit that the Petersen *et al.* and Castellino *et al.* references do not teach a variant consisting of the 207 carboxy-terminal amino acids of human plasminogen. Applicants also point out that plasminute corresponds to variant of human plasminogen. Specifically, amino acids 1 to 207 of plasminute are identical to amino acids 604 to 810 of plasminogen. The subject application relates to factors that selectively interact with an infectious isoform of the prion, but not with a normal, non-infection isoform of the prion. The factor may correspond to a fragment of human plasminogen. Applicants respectfully assert that the Aguzzi *et al.* reference does not teach a fragment consisting of the 207 carboxy-terminal amino acids of human plasminogen. In addition, Applicants submit that numerous fragments can be generated from an 810 amino acids long protein. The Aguzzi *et al.* reference does not suggest to generate a plasminogen fragment consisting of the 207 carboxy-terminal amino acids of human plasminogen. Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl
Attachment: Form PTO/SB/08 (1 page)

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,095	11/13/2001	Stephane Bejanin	91.US5.DIV	1774

23557 7590 06/01/2005

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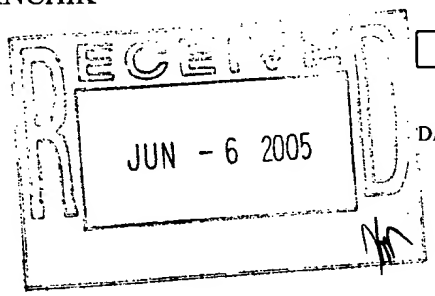

EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

AUG - 7 2006

Supplemental **Notice of Allowability**	Application No. 09/992,095	Applicant(s) BEJANIN ET AL.	
	Examiner Sheridan L. Swope	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *April 15, 2005*.

2. ☒ The allowed claim(s) is/are *30,31,34,36 and 53-59*.

3. ☒ The drawings filed on *13 November 2001* are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *10/000,489* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

AUG - 7 2006

5.0.8

This supplemental Notice of Allowance replaces the Notice of Allowance mailed May 19, 2005 and serves only to remove the Examiner's amendment to page one of the specification in the action of May 19, 2005.

DETAILED ACTION

Applicant's response, on April 15, 2005, to the First Action on the Merits of this case mailed November 17, 2004, is acknowledged. It is acknowledged that applicants have cancelled Claims 32, 33, and 35, amended Claims 30, 31, 34, and 36, and added Claims 53-59. Claims 30, 31, 34, 36, and 53-59 are pending. Claims 53-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention, there being no allowable generic or linking claim. Claims 30, 31, 34, and 36 are hereby reconsidered.

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Specification

For page 7, line 6, of the specification, replace –Sequences are presented in the accompanying Sequence Listing.– with – GENSET polypeptide and polynucleotide sequences are presented in the accompanying Sequence Listing as SEQ ID NO: 1-112.–.

Claims

For Claim 30, line 2, Claim 55, line 2, Claim 56, line 2, and Claim 59, line 2, replace –comprising– with –consisting of–.

For Claim 31, line 1, replace –A Plasminute protease– with – An isolated Plasminute protease–.

Rejoinder

Claims 30, 31, 34, and 36 are directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), Claims 53-59, directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Process Claims 53-59 are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Authorization for this examiner's amendment was given in a telephone interview with Frank C. Eisenschenk on May 13, 2005.

Allowable Subject Matter

Claims 30, 31, 34, 36, and 53-59 are allowed.

The following is an examiner's statement of reasons for allowance:

All elected Claims, 30, 31, 34, 36, and 53-59, are limited to the isolated polypeptide of SEQ ID NO: 54 and methods of digesting a protein using said polypeptide. The prior art does not anticipate or render obvious the polypeptide of SEQ ID NO: 54. The utility of the polypeptide set forth by SEQ ID NO: 54 as a protease with the activity of plasmin is credible based on the following. The polypeptide of SEQ ID NO: 54 consists of residues 585-791 of plasminogen (Petersen et al, 1990; IDS). Inactive plasminogen is cleaved to the active polypeptide, plasmin, consisting of residues 562-791 of plasminogen and including the catalytic triad of His^{603}, Asp^{646}, and Ser^{741} (Petersen et al, pg 6104, parg 2). Since SEQ ID NO: 54 is

missing only 22 residues from the N-terminus of plasmin and comprises the catalytic triad, a person of ordinary skill in the art would believe that it is more likely than not that the polypeptide set forth by SEQ ID NO: 54 has the same activity as plasmin. It is known in the art that plasmin digests the insoluble fibrin clot into soluble fragments during tissue repair and recanalization (Petersen et al, pg 6104, parg 1).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Sheridan Lee Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600

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CERTIFICATE OF CORRECTION

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APPLICATION NO. : 09/992,095

ISSUE DATE : January 24, 2006

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